ANNALS
OF THE
RHEUMATIC DISEASES

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The Official Journal
of the
EMPIRE RHEUMATISM COUNCIL

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ANNALS

OF THE

RHEUMATIC DISEASES

THE OFFICIAL JOURNAL OF

THE EMPIRE RHEUMATISM COUNCIL

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Owing to war conditions and the need for economy in paper, two issues only of "Annals of the Rheumatic Diseases" will be published this year, instead of four. Subscribers' payments will be adjusted accordingly.

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ANNALS
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EDITORIAL

THE Editors regret that they have again to apologize for delay in the appearance of the Annals owing to war conditions. It is the intention of the Empire Rheumatism Council that publication shall continue even in the face of these difficulties, and no doubt is felt that this policy will command the approval and support of all subscribers.

It is with the greatest satisfaction that they welcome the addition of Dr. Loring Swaim, of the American Rheumatism Association, to the Editorial Committee.

THE USE OF THE SULPHONAMIDE GROUP OF DRUGS IN THE TREATMENT OF TONSILLITIS DUE TO THE BETA-HÆMOLYTIC STREPTOCOCCUS AND IN ACUTE RHEUMATIC FEVER*

By W. A. HOPKINS

Introduction

Over forty years have elapsed since Poynton and Paine (1900) first indicted streptococcal infection as the cause of rheumatic fever, and since then numerous investigations have been carried out which go far to support their views. Owing to the difficulty which exists in reproducing the disease experimentally, conclusive evidence that this organism is directly responsible is still lacking, but sufficient data have been accumulated to show that a definite relationship exists between the two. The literature on the subject is voluminous, but recent significant work in support of the streptococcal theory has been carried out by Green (1939), who isolated hæmolytic streptococci from the heart valves in eight out of nine cases of fatal acute rheumatic fever. In five of these cases hæmolytic streptococci were isolated from throat cultures during life, and these were serologically identical with those isolated from the cardiac lesions. Collis (1939) and Thompson and Innes (1940) have reported similar findings. Additional support from the serological aspect has been given by Todd (1932), who found a rise in the antistreptolysin titre in a high proportion of cases of acute rheumatism; since then, Coburn and Pauli (1932, 1935) and Green (1941, A) have carried out work confirming Todd's findings. If the view that the hæmolytic streptococcus is of ætiological significance in acute rheumatic fever is accepted, it is reasonable to suppose that this organism gains access to the body through the most obvious route, the naso-pharynx, and numerous observers have noted the relationship which exists between streptococcal sore throat and acute rheumatism. Glover and Griffith (1931) found that in a number of schools where naso-pharyngeal infection with the hæmolytic streptococcus had been

* Received for publication December 15, 1941.

epidemic there followed outbreaks of acute rheumatism; and so long ago as 1884 Haig Brown (Coburn and Pauli, 1932) described an epidemic of tonsillitis among a group of public-school boys which, after a time lag, was followed by an outbreak of acute rheumatism. Green (1941, B) has shown that in a community where hæmolytic streptococcal infection was epidemic the distribution of acute rheumatism resembled that of tonsillitis, but was unlike that of any other disease, and, furthermore, that the peak incidence of the former occurred some six weeks later than that of the latter. The same observer (1938) found that in a series of two hundred cases of acute or subacute rheumatism 58 per cent. had hæmolytic streptococci in the naso-pharynx at the onset of their illness—a figure much above that to be expected in a series of healthy controls.

With such strong evidence, circumstantial though it may be, in support of the view that the hæmolytic streptococcus is of ætiological significance in acute rheumatic fever, and that the disease is commonly preceded by an attack of streptococcal tonsillitis, it was obvious from the first that the introduction of new chemotherapeutic agents in the form of the sulphonamide group of drugs might prove of the greatest importance in the treatment of a condition which hitherto it had only been possible to treat empirically and, it must be admitted, unsuccessfully. Two approaches to the therapeutic problem seemed feasible: if this new drug proved successful in the treatment of streptococcal tonsillitis, there was reason to hope that the matter would be solved prophylactically; and there was also reason to hope that the drug might prove to be efficacious in the treatment of acute rheumatism itself.

Domagk's (1935) publication on the use of prontosil in the treatment of experimental streptococcal infections of mice was closely followed by numerous papers dealing with the use of the drug in various infectious processes affecting the human body, and some six months after Domagk's original article Roth (1935) reported favourably on the use of prontosil in hæmolytic streptococcal infections. Since then a large volume of experimental and clinical data has been built up concerning the use of this drug and similar compounds which have been synthesised more recently. In a voluminous literature there are numerous references concerning their value or otherwise in the treatment of both streptococcal sore throat and acute rheumatism.

Encouraging and, in some cases, enthusiastic reports of the value of these drugs in the treatment of tonsillitis due to the hæmolytic streptococcus appeared at first, and continued to do so for some time. In a series of thirty-nine cases of streptococcal tonsillitis, Smith (1937) used prontosil album (*p*-amino-phenyl sulphonamide) in twenty-two cases and proseptasine (*p*-benzyl-amino benzene sulphonamide) in the remaining seventeen. Hæmolytic streptococci were isolated from throat cultures in thirty-one of these cases. Using an initial daily dosage of 7·2 gms. of the former drug and, in some instances, as much as 12·5 gms. of the latter, he found that in twenty-six of these cases the response was satisfactory, nineteen having normal temperatures within twenty-four hours and the remainder within thirty-six hours. He also noted that "pain in the throat and general discomfort soon disappeared" and that in "no case were there any new complications." Perkins (1937) was also enthusiastic, and, using prontosil rubrum in a series of ten cases with ten controls, he found that both the period of hospitalisation and the period of convalescence were reduced. It is to be noted, however, that hæmolytic streptococci were only isolated from two of the treated cases and not at all from the controls. Successful results were also published by Basman and Perley (1937), by Peters and Havard (1937), by Kramer (1936), and by Long and Bliss (1937). Other observers noted that the use of the drug materially reduced the time for which throat cultures remained positive, and Gallagher (1937), in a series of thirty-three cases, published a report to this effect. The carrier problem was also dealt with by Brenneman (1937), who found that in almost every case carriers of hæmolytic streptococci became negative shortly after treatment with sulphanilamide was instituted He also noted that one to six days after the drug was discontinued the throat swabs became positive again. By no means all of the early observations were equally enthusiastic, and several less convincing reports appeared. Watson Williams (1937) was of the opinion that the results were no better than when sodium salicylate was used; McIntosh *et al.* (1937) reported unconvincing results; and Whitby (1937) had seven successes and two failures. That patients already receiving treatment with sulphonamides were still liable to contract tonsillitis was shown by Kenny *et al.* (1937), who reported two such cases. So far no properly controlled series of cases had appeared in the literature, but in

1940 Rhoads and Afremow published details of a group of thirty-one sulphanilamide-treated patients with thirty-six controls. These observers found that the use of the drug did not reduce "the severity of the symptoms, shorten the period of incapacity, reduce the incidence of complications, or reduce the duration of the carrier state." In addition they noted that, using an average daily dose of 3·6 gms. and attaining an average blood level of 6·38 mgms. per 100 c.c., toxic manifestations of the drug other than the usual cyanosis occurred in one-half the cases in which sulphanilamide had been administered.

A search of the literature shows that reports of the value of the sulphonamides in the treatment of acute rheumatism are few and far between. However, when the drug was first introduced a few favourable reports appeared; using "streptozon," Veil (Recknagel, 1935) found that cases of acute rheumatism improved and that the blood sedimentation rate was lowered, and Klee and Romer (1935) were favourably impressed with the use of prontosil in similar cases. Most observers, however, were of the opinion that no beneficial results could be expected from the use of these drugs; Massell and Jones (1938), in a series of fifty-eight patients, found that sulphanilamide did not produce any symptomatic relief or shorten the course of rheumatic fever; Hench (1938) and his co-workers came to the conclusion that not only was sulphanilamide of no value, but that it seemed to be particularly toxic in this condition; and Swift *et al.* (1938) drew similar conclusions from a careful study of eight cases. They noted also that, of the eight patients, the antistreptolysin curve for six was indicative of recent infection with hæmolytic streptococci, the other two being equivocal, and that there was no evidence that the formation of antistreptolysin was in any way influenced by the exhibition of the drug. In this connection it is interesting to note that Green (1941, C), in a study of the effect of prontosil on the production of antistreptolysin O in rabbits, found "no evidence of inhibition or stimulation of antibody response" following the use of the drug.

Although the matter is outside the scope of this paper, mention must be made of the use of the sulphonamide group of drugs in preventing recurrence of rheumatic fever. Thomas and France (1939) carried out studies on this aspect of the problem during the years 1937 and 1938 with encouraging results, and Coburn and Moore (1939, 1940, 1941), in a very carefully followed

series of cases, found that a level of sulphanilamide in the blood of about 40 micrograms, maintained throughout the school year, protected against streptococcal pharyngitis and rheumatic recurrences. Furthermore, they found that withdrawal of the drug from one hundred of these patients resulted in 39 per cent. developing streptococcal pharyngitis, and of this 39 per cent. 40 per cent. developed rheumatic recrudescences. The importance of this work can hardly be overestimated.

My interest in the use of the sulphonamide group of drugs in the treatment of tonsillitis and acute rheumatic fever was aroused in 1939, at a time when a number of patients suffering from one or other of these conditions came under my care. They were drawn from a community of young male adults whose physical fitness was above the average of that of the general population, who lived under the same environmental conditions, and who were under constant medical supervision. This last meant that the minimum of delay ensued between a man reporting sick and his admission to hospital. The results of this investigation will be reported in two parts, the first dealing with the treatment of tonsillitis due to the hæmolytic streptococcus, and the second with that of acute rheumatic fever.

(A) Tonsillitis.—Alternate patients were placed on sulphonamide therapy. As experience during the few months previous to the study had shown that over 80 per cent. of the patients admitted to the hospital suffering from tonsillitis harboured beta-hæmolytic streptococci in their throats, it was decided to institute therapy immediately on their arrival in the ward and to exclude from the series those whose throat swabs proved negative for this organism. Others excluded from the series were patients who had suffered from symptoms for over forty-eight hours and those who were afebrile on admission to hospital. Throat swabs were taken immediately on admission to the ward and before any form of therapy, either local or general, was instituted. These swabs were applied to a blood-agar plate containing 10 per cent. horse blood, spread in the usual manner, and incubated under aerobic conditions at 37° C. for twenty-four hours. The cultures were then examined for colonies showing a clear ring of hæmolysis, and such colonies were picked off into broth which was incubated at 37° C. for sixteen hours, when the presence of hæmolysin was tested for. Only those patients whose cultures yielded typical colonies which

on subculture into broth gave a positive " tube test " are included in the series. Throat swabs were taken again after the local symptoms and pyrexia had subsided, and at intervals thereafter, until the cultures yielded negative results. The series comprises forty-nine treated patients with fifty controls, and the initial symptomatology of all patients was very similar. In almost every case the attack started with headache, severe sore throat and general prostration. A proportion of patients complained of attacks of shivering, and a minority of general body aches and pains. Examination on admission to hospital revealed pyrexia ranging between 100° and 103·5° F., acute pharyngeal inflammation and exudation, and, in almost all cases, cervical adenopathy. As has been said, alternate patients were treated with sulphonamides, the control group receiving aspirin in 10-grain doses three times a day. Apart from this, both groups received exactly similar treatment—*i.e.*, rest in bed until the temperature had been normal for three days, a light diet, and glyco-thymoline gargles. Two drugs—colsulanyde (para-amino benzene sulphonamide) and May and Baker " 693 " (sulphapyridine)—were used in the treated group, twenty-five patients receiving the former and twenty-four the latter. The dosage employed was uniform, 2 gms. being given four-hourly for four doses and thereafter 1 gm. four-hourly until the temperature was normal, when the amount was reduced to 1 gm. three times a day. Treatment was discontinued when the patient had been afebrile for forty-eight hours. In order that the blood concentration of the drug might be maintained adequately, patients were awakened during the night for their earlier doses. In assessing the results of treatment the following factors were taken into consideration: (1) duration of fever; (2) the number of days spent in hospital; (3) the duration of local manifestations (pharyngeal inflammation, exudate, and cervical adenopathy); (4) the length of time for which throat swabs remained positive; and (5) the occurrence of complications. The results obtained are shown in the following table; complicated cases are excluded, as the inclusion of such figures as eighty-six days' hospitalisation due to acute rheumatism supervening would grossly distort the general picture.

From the table on page 239 it will be seen that the average number of days' fever in the treated groups of cases was 2·4, as against 2·0 in the control group; that the average number of days spent in hospital was 9·0 as against 7·6; that the duration of local

	Colsulanyde-treated Group (21 uncomplicated, 4 complicated cases).	*M. and B. 693 treated Group* (19 uncomplicated, 5 complicated cases).	*Control-Group* (43 uncomplicated, 7 complicated cases).
Average duration of fever (in days) ..	2·2	2·7	2·(
Average number of days spent in hospital	8·5	9·6	7·6
Average duration of local manifestations (in days) ..	3·3	3·3	3·1
Average duration of positive throat swabs (in days)	6·1	6·3	5·1
Percentage of complicated cases ..	16	20·8	14

manifestation was similar in both groups of cases; and that hæmolytic streptococci remained in the throat for a day longer in the treated group. The incidence of complications was some 4·4 per cent. greater in the treated group. A total of nine complications occurred in the treated group of forty-nine patients the percentage being slightly higher in those treated with sulphapyridine. These complications were as follows: Five cases of peritonsillar abscess, two cases of persistent tachycardia, and two cases of rheumatic fever which supervened during the patients' stay in hospital. In neither case was there a previous history of acute rheumatism. In the control group of fifty patients there were only seven complications—four cases of peritonsillar abscess, two cases of persistent tachycardia (tachycardia was considered to be a complication when the pulse rate remained above 90 for over a week in the absence of pyrexia), and one case of otitis media. The general impression gained was that on the whole those complications encountered were less severe in the untreated group of cases.

In spite of the relatively high dosage employed, toxic reactions in the sulphonamide-treated group were conspicuous by their absence. Cyanosis was of common occurrence, and, in addition, some 40 per cent. of those patients who received sulphapyridine suffered from vomiting. It is felt, however, that these reactions are not contra-indications to the continued use of the drug. Apart from these, the only other complication noted was the occurrence of a toxic rash four days after therapy had been instituted. There were two cases of persistent tachycardia,

which may or may not have been due to the drug; it is to be noted that two such cases occurred in the control group as well. Leucopænia did not occur in any of the cases.

(B) Acute Rheumatic Fever.—Twelve cases of acute rheumatic fever were treated chemotherapeutically, half with M. and B. 693 and half with colsulanyde. Of these, nine were patients admitted suffering from their first attack and in whom no previous form of therapy had been employed; the remaining three were patients who were already in the ward and who developed rheumatic recrudescences. In view of the unfavourable results obtained in all the cases in the series, no attempt will be made to make any comparison with a control group. The dosage of the drug employed was similar to that used in tonsillitis—*i.e.*, 2 gms. four-hourly until 8 gms. had been given, then 1 gm. four-hourly until a total of some 20 to 25 gms. had been attained. In addition, patients were treated with absolute rest in bed and simple palliative local measures. The extent of the lack of success obtained can be seen from the following précis of the case notes.

Case 1.—B. D., aged sixteen, admitted with a three days' history of pain in his left leg and left knee joint. He reported sick the day before admission, and his previous treatment had consisted of rest in bed only. There was no history of any previous attack of rheumatism. On admission the patient presented the typical picture of acute rheumatism, with sweating, pyrexia of 101° F., and polyarthritis, the left knee and right ankle joints being affected. He was ordered sulphapyridine 2 gms. four-hourly. During the next four days his condition became steadily worse; the left wrist, left ankle, right wrist and right shoulder joints became affected in turn, being painful, swollen, hot and acutely tender. No fall in temperature was noted. On the sixth day of hospitalisation, when the patient had had 20 gms. of the drug, its use was discontinued and salicylate therapy was instituted. Following this, his condition improved rapidly; his temperature fell to normal, and within three days all joint pains and swellings had cleared up. On the eleventh day of his illness early signs of carditis were noted, and six weeks later systolic murmurs were still present at apex and base, and the blood sedimentation rate was still grossly abnormal. Hæmolytic streptococci were isolated from his throat on admission.

Comment.—Full doses of sulphapyridine, with a total amount of 20 gms., failed to influence the course of a typical case of acute rheumatism in any way, nor was the onset of carditis prevented. The only toxic reaction to the drug was occasional vomiting.

Case 2.—F. J., aged nineteen. Two days before admission he suffered from vague pains in his legs from the knees downwards, and the day before admission he found difficulty in standing, owing to the pain in his feet. There was no previous history of rheumatism. On admission both ankle

joints were swollen, hot and tender; temperature was 102·4° F., and pulse rate 100. Sulphapyridine 2 gms. four-hourly was prescribed, and this drug was continued until a total of 20 gms. had been given. During the next five days no improvement in his condition was noted; his temperature remained high, polyarthritis continued, and on the third day of his illness signs of carditis presented themselves. On the fifth day of his illness he developed acute nephritis, with albuminuria, hæmaturia, a low urinary specific gravity, slight œdema, a moderate degree of hypertension, and a blood urea of 84 mgms. per 100 c.c. This complication cleared up slowly and was followed by a moderate degree of hypochromic anæmia. Two months after the patient's admission to hospital well marked signs of carditis were still present and the corrected blood sedimentation rate (Wintrobe's method) was 23 mm. at one hour.

Comment.—Twenty gms. of sulphapyridine was not followed by any improvement, nor did it prevent the onset of carditis. Cyanosis was marked and vomiting was troublesome during the period in which the drug was used, and the case was complicated further by the occurrence of acute nephritis.

Case 3.—G. I., aged twenty-one. Two days before admission he suffered from pain and swelling in his right wrist joint. The following day the pain and swelling spread to his left wrist and finger joints, and he reported sick. There was no previous history of rheumatic fever. On admission, both wrist joints and the interphalangeal joints of his left hand were swollen and tender, and the patient's temperature was elevated to 99·6° F. Colsulanyde 2 gms. four-hourly was prescribed, and this drug was continued until a total of 18 gms. had been given. No improvement followed; new joints became involved and low-grade pyrexia continued. Carditis did not ensue. Apart from cyanosis, no toxic manifestations followed the use of the drug. At the end of a month, when it became necessary to transfer the patient to another hospital, there was still evidence of rheumatic activity in the shape of a raised blood sedimentation rate.

Comment.—As compared with several similar patients in the ward, it was not felt that this patient derived any benefit from his treatment. Carditis did not occur, but neither was this complication found in a number of similar cases which had been treated with salicylates.

Case 4.—E. G., aged twenty. Admitted to hospital with a history of having suffered from a sore throat for one day. No previous history of note was elicited. On admission to hospital, temperature was 103·2° F. and pulse rate 120. Fauces were grossly inflamed, and the left tonsil was covered with a yellowish exudate. A throat swab yielded hæmolytic streptococci. There was little change in the patient's condition during the next two days; both pyrexia and tachycardia persisted, and his throat remained sore, inflamed and septic. On the third day of his illness he complained of pain in his left wrist joint, which on examination was found to be swollen, inflamed and tender. At this time there was pyrexia of 103·5° F. and a pulse rate of 120. Colsulanyde therapy was instituted, 2 gms. being given four-hourly. On the following day the patient's temperature had dropped to 99·4° F., with a pulse rate of 100, and his throat was much easier. No improvement, however, was noted in his wrist joint. Following this, the typical rheumatic picture with low-grade

pyrexia and fleeting polyarthritis presented itself, and on the eighth day of the patient's illness signs of carditis were noted for the first time. At the end of a month, when he was transferred to another hospital, signs of carditis were still present.

Comment.—This patient developed acute rheumatism during an attack of streptococcal tonsillitis. A full course of 20 gms. of sulphanilamide failed to ameliorate the symptoms or to prevent the onset of carditis.

Case 5.—S. S., aged nineteen. Admitted to hospital with a history of having suffered from fleeting joint pains for several days. There was a history of an attack of rheumatic fever five years previously, with a recrudescence of activity three years later. On the second occasion the patient was ill for five months, and his heart was mentioned during the course of his illness. Following this bout, he was advised to avoid strenuous exercise, but he stated that he was able to cycle eighty to a hundred miles in a day without any fatigue or distress. On admission to hospital, temperature was 100° F., pulse rate 100, and there was polyarthritis affecting both elbow joints, the left ankle joint and the interphalangeal joints of the left hand. In addition there was evidence of cardiac involvement with left ventricular enlargement (apex beat in the fifth space, 15 centimetres from the middle line), a forcible cardiac impulse, and the characteristic bruits of aortic incompetence. In the hope of limiting the attack, colsulanyde was prescribed in doses of 2 gms. four-hourly. The patient's condition remained unaltered for forty-eight hours, but at the end of that time he complained of præcordial pain. The following day signs of pericarditis were present, and twenty-four hours later a diagnosis of pericardial effusion was made. This was confirmed radiologically. There followed a stormy illness, with numerous recurrences of pyrexia and polyarthritis in addition to the cardiac complications. Sulphanilamide therapy was discontinued when a total of 18 gms. had been given.

Comment.—Sulphanilamide failed to alter the course of a rheumatic recurrence, failed to prevent the onset of pericarditis, and was without any beneficial effect in this complication.

Case 6.—M. A., aged eighteen. Admitted with a two days' history of stiffness in his legs and gradually increasing pain in both knee joints, left foot and right wrist. He gave a history of having had a severe attack of tonsillitis a month previously. On admission, there was pyrexia of 101·6° F., with a pulse rate of 104, marked sweating, and polyarthritis affecting both knee joints and the left ankle joint. Sulphapyridine 2 gms. four-hourly was prescribed. Pyrexia, tachycardia and polyarthritis continued, and on the third day of the patient's illness signs of carditis were noted. The drug was withdrawn when a total of 20 gms. had been given, and sodium salicylate in maximal doses was substituted in its place. Following this the patient's temperature fell to normal and his arthritis subsided. During the next six weeks there were several minor recrudescences, with short bouts of a low-grade pyrexia coupled with polyarthritis. Evidence of carditis was still present when the patient was sent to another hospital at the end of seven weeks.

Comment.—Sulphapyridine failed to benefit a case of acute rheumatism which responded promptly to salicylate therapy. Nor did the drug prevent the onset of carditis.

CASE 7.—C. S., aged sixteen. Admitted with a two days' history of pain and swelling in his right foot and ankle. He gave a history of an attack of sore throat two months previously. On admission, there was pyrexia of 99·2° F., with a pulse rate of 116, and arthritis of the right ankle joint was found to be present. Colsulanyde in 2-gm. doses four-hourly was prescribed, and was continued until a total of 32 gms. had been given. The patient continued to suffer from fleeting polyarthritis, an irregular low-grade pyrexia persisted, and the pulse rate remained unduly high. On the tenth day of his illness his temperature was still 100° F., with a pulse rate of 112, and joint pains and swellings were still present. Two months later there was evidence of continued rheumatic activity in the shape of a raised B.S.R. (corrected B.S.R. 26 mm. at one hour), and tachycardia still persisted.

Comment.—Thirty-two gms. of sulphanilamide had no effect on the course of a case of acute rheumatism, nor did it prevent the onset of carditis as shown by persistent tachycardia.

CASE 8.—T. F., aged seventeen. Admitted with twenty-four hours' history of a sore throat and pains in his elbow joints. There was no history of any previous attack of rheumatism. On admission there was pyrexia of 100° F., with a pulse rate of 88, slight faucial inflammation (a throat swab yielded no hæmolytic streptococci), and arthritis of both elbow joints. Colsulanyde was prescribed and was continued until a total of 34 gms. had been given. Pyrexia continued for four days and fleeting arthritis for six days, at the end of which time the patient was afebrile and symptom-free. A week later there was a recurrence of activity with pyrexia and arthritis, and this bout continued for a further eight days. Signs of carditis were noticed during this bout, and two months later examination of the heart showed left ventricular enlargement with systolic murmurs at the apex and base.

Comment.—A full course of sulphanilamide failed to influence the course of a typical case of acute rheumatism, or to prevent the onset of carditis.

CASE 9.—J. J., aged eighteen. Admitted with forty-eight hours' history of generalised body stiffness and pains in both knee joints. On admission there was pyrexia of 101°, with a pulse rate of 120, sweating, and polyarthritis affecting both knee joints and the left ankle joint. Sodium salicylate in 20-grain doses four-hourly was prescribed. Fever and polyarthritis continued for three days, but then responded to salicylate therapy. A week later there was a recurrence of pyrexia and polyarthritis; this bout in its turn responded to salicylates, and when it had ended colsulanyde in 1-gm. doses four-hourly was prescribed, in the hope that a further recrudescence might be prevented. Four days later a further recurrence, with pyrexia of 101° F. and polyarthritis, manifested itself. The dose of colsulanyde was increased to 2 gms. four-hourly, but no improvement followed. On the contrary, there was continued pyrexia, all joints of the upper and lower limbs became affected in turn, and signs of acute carditis were noted. Sulphanilamide therapy was continued for another three days, at the end of which time it was stopped, as it was obvious that the patient, instead of improving, was getting worse. There followed a protracted illness with numerous recurrences of pyrexia and arthritis, together with severe pancarditis. At the end of three months,

when the patient was transferred to another hospital, he was still being nursed as a strict bed case; evidence of severe pancarditis was still present, and the corrected B.S.R. was 26 mm. at one hour.

Comment.—Sulphanilamide failed to prevent a rheumatic recurrence, and had no beneficial effect on the recurrence that took place.

Case 10.—T. P., aged seventeen. Admitted with three days' history of vague pains in his ankle joints. On admission there was pyrexia of 101° F., with a pulse rate of 92, sweating, and arthritis affecting both ankle joints. Sulphapyridine 2 gms. four-hourly was prescribed. Pyrexia, tachycardia and fleeting polyarthritis persisted, and sulphapyridine was discontinued when a total of 18 gms. had been given. Salicylate therapy was substituted in its place, and the use of this drug was followed by rapid improvement. Signs of carditis were noticed at the end of ten days' illness, and at the end of three months' illness, when the patient was transferred to another hospital, examination of the heart revealed left-sided enlargement with systolic murmurs at the apex and base.

Comment.—This case is comparable to Case No. 1. No improvement followed the use of sulphapyridine in a case of acute rheumatism, nor was the onset of carditis prevented.

Case No. 11.—H. F., aged twenty. Admitted with acute bronchitis. During the course of his illness typical acute rheumatism with pyrexia, sweating, and polyarthritis developed, and was treated with sodium salicylate. Carditis appeared a week after acute rheumatism was first diagnosed. Three weeks later sulphapyridine 1 gm. T.D.S. was prescribed, in the hope that a recurrence might be prevented. Four days afterwards there was a recrudescence of activity with pyrexia and arthritis; the dose of sulphapyridine was increased to 2 gms. four-hourly, but the symptoms persisted. The drug was withdrawn when a total of 22 gms. had been given; salicylates were reinstituted, and, following this, pyrexia and arthritis subsided.

Comment.—Sulphapyridine failed to prevent a rheumatic recrudescence or to influence the course of the recrudescence that did appear.

Case 12.—H. J., aged eighteen. Admitted with a history of pain in both feet and both knees of forty-eight hours' duration. On admission he was afebrile, with a pulse rate of 84, and there was arthritis affecting both ankle joints and the right knee joint. Sulphapyridine 2 gms. four-hourly was prescribed. Following this, his temperature rose to 101° F., with a pulse rate of 104, and fleeting polyarthritis persisted. The pyrexia and local symptoms continued unabated during the next few days, during which time sulphapyridine was persevered with. When a total of 22 gms. had been given, the drug was discontinued and salicylate therapy was substituted in its place. This was followed by rapid improvement; the patient's temperature fell to normal within three days, and his arthritis cleared up. At the end of a month, when it became necessary to transfer him to another hospital, his pulse was still unduly rapid, but no other signs of carditis were noted.

Comment.—Twenty-two gms. of sulphapyridine was given without beneficial effect in a case of acute rheumatism, which responded rapidly to salicylate therapy.

Discussion

Perusal of these case notes will show that in no instance did sulphanilamide or sulphapyridine have any beneficial effect on the rheumatic process. The use of these drugs was not followed by any fall of temperature, polyarthritis was not relieved, and the onset of carditis was not prevented. Although full doses of the drugs in question were given, toxic reactions to their use were not troublesome. A degree of cyanosis was apparent in most patients; vomiting was troublesome in two of the sulphapyridine-treated cases, but apart from this no anxiety was caused. Leucopænia did not develop in any case; on the other hand, the leucocyte count tended to rise rather than to fall.

Conclusions

(A) Streptococcal Tonsillitis.—1. A series of forty-nine sulphanilamide- or sulphapyridine-treated cases is compared with fifty controls.

2. No beneficial effect followed the use of these drugs in the treated series of cases. As compared with the control group there was no shortening of the period of pyrexia, of the duration or severity of the local manifestations, or of the period of hospitalisation.

3. The incidence of complications was found to be greater in the treated group than in the control group.

4. That streptococcal tonsillitis can develop in patients already undergoing intensive sulphapyridine treatment is shown by the occurrence of two such patients in this series.

5. The carrier state was not influenced by the use of these drugs.

6. Toxic reactions to the use of these drugs were not found to be troublesome.

(B) Acute Rheumatism.—1. A series of twelve cases of acute rheumatism was treated with sulphanilamide or sulphapyridine. Of these, nine were patients suffering from their first attack and three were patients suffering from recrudescences.

2. In no case was the use of these drugs followed by any fall in temperature or amelioration of arthritis.

3. The withdrawal of these drugs and the substitution of salicylates in their place was followed by immediate improvement.

4. Carditis was not prevented.

5. Toxic reactions to the use of the drug, other than cyanosis, were not found to be troublesome.

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AN EPIDEMIC MYALGIA DISTINCT FROM BORNHOLM DISEASE, WHICH CHIEFLY AFFECTED THE MUSCLES OF THE NECK*

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At the present time Bornholm disease is the only recognised condition characterised chiefly by muscle pain which occurs in epidemic form. Indeed, the terms "epidemic myalgia" and "Bornholm disease" are used synonymously by many writers. Massell and Solomon[1] (1935) have suggested, however, that the common condition of "stiff neck," or acute torticollis, represents another form of epidemic myalgia, and have reported the occurrence of fifty-two cases of "stiff neck" within three months in a group of three hundred persons, an attack rate of 17·3 per cent. Clinically their cases bore a close resemblance to those which are described in this communication. Smith[2] (1937) reported a series of cases of "cervical myalgia" which occurred one winter among the boys at Rugby School, but he expressed the belief that these represented a form of Bornholm disease.

During the summer and fall of 1941 "stiff neck" seemed prevalent in various parts of Southern England. Accordingly, attempts have been made to accumulate accurate data on the incidence of this condition. The following is a description of a study carried out on a group of factory workers in November, 1941.

Method of Survey and Population Studied

The population examined consisted of the employees of a piston-ring factory. The factory building, situated on the outskirts of a small city, contained one large machine room, dimensions 160 by 50 feet; an inspection room, 50 by 15 feet; and two small offices. At the time of the survey the employees were: two office workers, eleven inspectors, and one hundred and fifty machine workers; eighty-two of these persons were males and eighty-one were females. The work of the factory was done in two shifts, the members of the day-shift working from 7.30 a.m. to 7 p.m., those of the night-shift from 7.30 p.m.

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to 7 a.m. During each shift there was a thirty-minute recess for tea and a sixty-minute lunch recess. These meals were eaten in the inspection room. Thus there was opportunity for rather close contact between all of the workers within each shift; but, on the other hand, there was little direct contact between the workers of the night-shift and those of the day-shift. The initial survey was made on November 19 by a group of public health nurses working under the supervision of the authors. Each employee of the factory was interviewed, and the information was entered on the following form:

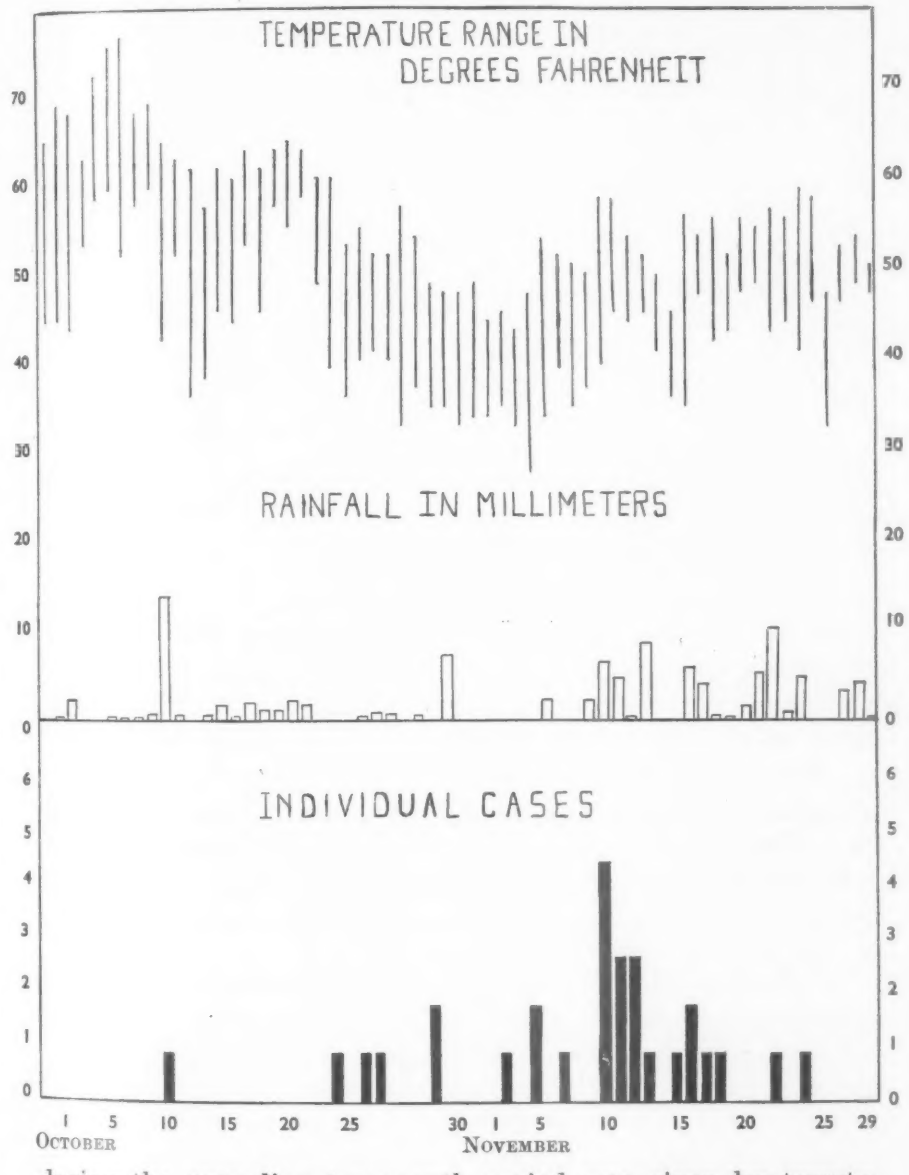
Name. Age. Sex. Occupation.
Have you had any pain or stiffness in the neck or shoulders within the past six weeks ?
If " Yes."
Date of onset.
Character of pain.
Location of pain (indicated on a diagram of the head and shoulders).
Ability to turn head.
Local soreness.
Did you have associated with it any of the following?
1. Headache. 2. General discomfort. 3. Fever. 4. Chilliness. 5. Common cold.
Measures of relief.
Symptoms aggravated by.
Duration of symptoms.
Did symptoms interfere with normal activities ?
What do you think caused them ?
Ever have this previously ?
How often ?
When ?
Were others affected at the same time ?
Address since October 1.
Present residence.
Do you know anyone who has had " stiff neck " recently ?
If " yes," what is the association ?
Date.
History taken by.

This form enabled the survey to be completed rapidly and without disturbance of factory routine. In cases where persons were experiencing symptoms at the time of the initial survey, follow-up inquiries were made. Because of the need for this information the study was continued for two weeks more than originally intended, thus covering a period of two months.

Results of Survey

1. *Attack Rate.*—Of the one hundred and sixty-three persons questioned, a history of pain or stiffness in the neck or shoulder

Daily Incidence of Myalgia in Relation to Temperature Variation and Rainfall.



during the preceding two-month period was given by twenty-nine individuals—twelve males and seventeen females. This gives an attack rate of 17·8 per cent.

2. *Distribution of Cases in Relation to Date of Onset and the Weather.*—The time relationship of the cases, according to the day of onset, is illustrated in Graph I and tabulated in Table I. Plotting the cases graphically gives a picture suggestive of an epidemic curve. The climatological data show that a period of cold weather preceded the time at which the case incidence was highest. The significance of this is not certain.

TABLE I.—DAILY INCIDENCE OF MYALGIA.*

Date.	*Number of Cases.*
October 10	1
,, 22	1
,, 24	1
,, 25	1
,, 29	2
November 3	1
,, 5	2
,, 7	1
,, 10	5
,, 11	3
,, 12	3
,, 13	1
,, 15	1
,, 16	2
,, 17	1
,, 18	1
,, 22	1
,, 24	1

3. *Age and Sex Distribution.*—As can be seen from Table II, the disease appeared to be more common in women than in men, seventeen cases among eighty-one, as compared with twelve cases among eighty-two, respectively. It should be pointed out that the age range of the two sexes is different, the average age of the women being twenty-six years, while that of the men was forty-two. From the small numbers studied in this particular population it is impossible to be certain whether the higher incidence of cases among women was due to a sex or age predilection of the disease.

4. *Previous Attacks.*—Fifteen of the twenty-nine affected persons gave a history of previous attacks; six of these had had one previous attack, and nine of them had had two or more. One man stated that he had suffered from "stiff neck" once a year for the past fifteen years. In five of the fifteen cases a previous attack had occurred during 1941, while five others had

* The survey and compiling of data were carried out by nurses of the Harvard Public Health Unit.

been affected during 1940. Of the one hundred and thirty-five persons who did not have any symptoms during the two-month survey period, thirty-four gave a history of one or more attacks of " stiff neck " at some previous time.

TABLE II.—DISTRIBUTION OF CASES OF ACUTE MYALGIA IN A GROUP OF FACTORY WORKERS, OCTOBER AND NOVEMBER, 1941.

	Age Group in Years.						*Total.*
	10–19.	20–29.	30–39.	40–49.	50–59.	60 and over.	
Males.							
Number in each age group	1	10	19	34	12	6	82
Cases of myalgia ..	0	0	4	6	1	1	12
Females.							
Number in each age group	11	52	12	3	2	1	81
Cases of myalgia ..	3	11	2	0	1	0	17
Total number of persons in each age group	12	62	31	37	14	7	163
Total number of cases of myalgia in each age group	3	11	6	6	2	1	29
Per cent.	25·0	17·7	19·4	16·2	14·3	14·3	17·8

5. *Type of Person Affected.*—Consideration of the residences of the affected persons showed only that they came from widely scattered districts, with no evidence of case grouping. Two of the patients stated that there had been cases of " stiff neck " among their associates outside the factory within recent weeks, while similar information was obtained from five of the one hundred and thirty-five non-affected persons. No particular group of employees within the factory had been affected predominantly, since cases occurred among machine workers, inspectors and office workers (see Table III). This wide distribution

TABLE III.—DISTRIBUTION OF CASES ACCORDING TO TYPE OF WORK DONE.

Classification.	*Number in Group.*	*Cases of Myalgia.*
Office workers	2	2
Inspectors	11	1
Machine workers	150	26
Totals	163	29

of cases among personnel doing various types of work is of interest in connection with the opinions of some of the patients

mentioned below, who thought of the disease as a direct result of their work. No difference was found in the attack rates in the day- and night-shifts (see Table IV).

TABLE IV.—ATTACK RATE OF MYALGIA ACCORDING TO FACTORY SHIFT.

Factory Shift.	*Number in Group.*	*Cases of Myalgia.*	*Attack Rate.*
Day	99	18	18·1
Night ..	64	11	17·2
Totals ..	163	29	—

6. *Patients' Opinions on Cause of Disease.*—Persons who had suffered from "stiff neck" during the survey period were asked for their explanation of the cause. A classification of their answers is given in Table V. Twenty of the twenty-nine persons blamed a "draught," five considered the condition due to the type of work done, one person ascribed it to the weather, and three persons said that they did not know.

TABLE V.—CAUSES OF MYALGIA AS GIVEN BY THE PATIENTS.

Causative Agents.	*No. of Individuals.*
Exposure to draughts	20
Type of work	5
Change in weather	1
Unknown	3
Total	29

CLINICAL FEATURES

Certain details of the clinical disease were obtained from the histories and from observation of persons seen during the acute stage. In a typical case the appearance was characteristic; the head was held stiffly, and in looking to the side the eyes or body were turned instead of the neck. Invariably there was pain in some part of the trapezius muscle, although in some instances other muscles, such as the deltoid or sternomastoid, were also involved. The portions of the trapezius which were the most frequent sites of pain were: a point on the superior margin of the muscle midway between the occiput and acromion, the occipital attachment, and the portion adjacent to the lower cervical spine. In a few cases pain extended to other sites, such as the arm, forearm, lumbar and gluteal regions. Multiple sites of pain were the rule, sixty-two painful areas having been charted in the twenty-nine cases. Involvement of the right and left

sides was almost equal (see Table VI). The pain was described as an "ache" by nineteen persons, as "sharp" by five, while the remaining five persons noted only a sensation of "stiffness."

TABLE VI.—LOCATION OF PAIN: 29 CASES OF MYALGIA.

Right side only	7
Right side and midline	3
Left side only	6
Left side and midline	4
Midline only	4
Left and right sides	2
Left and right sides and midline	3

Impairment of ability to turn the head was recorded in twenty-one cases. Only sixteen of twenty-nine affected persons gave a history of local tenderness when questioned, but, from our experience, it seems probable that careful examination during the acute stage would always reveal such areas. Interference with normal activity—at work or at home—was experienced by twelve persons. Of these only two had consulted physicians, the others obtaining relief from such measures as bed rest, local heat and aspirin. The duration of symptoms was from one to four days in eighteen cases; from five to ten days in four cases; from ten to fourteen days in four cases; twenty-one days in one case; and in the two reported below symptoms were still present at the time of writing, having existed for three weeks and two weeks respectively. General symptoms were not a prominent feature, patients as a rule feeling nearly normal except for pain in neck or shoulder. Fifteen persons gave a history of headache; this seemed in some instances to have been related to pain in the trapezius near its occipital attachment. Twelve of the twenty-nine individuals stated that they had had a common cold at the time of their "stiff neck," while four gave a history of fever.

In two persons the disease took a more severe form. One was a man, thirty-eight years of age, who at the time of the survey had been confined to bed at home for nine days. His illness had begun with pain in the right side of the neck and inability to turn the head. Associated with this there had been some general malaise and weakness. In succeeding days the pain had extended down to the lumbar, gluteal and hamstring

muscles on the same side. When interviewed again on December 2 he was out of bed, but still unable to work because of weakness and some residual pain. The other was a young woman of twenty-one, who was seen on November 22, the day of onset of her symptoms. At this time she described a dull aching pain in the region of the mid portion of the superior border of the left trapezius muscle. Pressure over the area caused pain. She held her head stiffly. There were no other complaints. She was seen again on November 24, when she was suffering from pain in the region of the left deltoid insertion. She also described numbness and tingling in the palm of her left hand, although there was no impairment of sensation by objective test. Blood examination showed a total leucocyte count of 10,200 per cu. mm., with 66 per cent. neutrophils, 33 per cent. lymphocytes, and 1 per cent. eosinophils. Erythrocyte sedimentation rate (100 mm. tube) was: 1 mm. in fifteen minutes, 3 mm. in thirty minutes, 9 mm. in forty-five minutes, and 13 mm. in sixty minutes. She had no elevation of temperature. The following day she complained of crampy pain in the arch of the left foot, and of "pins-and-needles" in that part. On November 26 the pain caused her to remain in bed at home. On November 28 she was transferred to the American Red Cross Harvard Field Hospital for further care. There was no fever, and she did not appear very ill. She still held her head stiffly. Areas of tenderness were found in the following parts: over the mid portion of the superior border of the left trapezius muscle, in the region of the insertion of the left deltoid, in the upper third of the flexor surface of the left forearm, and in the upper part of the left gluteus medius muscle. Physical examination was otherwise negative. Blood examination on December 1 showed: a total leucocyte count of 9,000 per cu. mm., of which 69 per cent. were neutrophils, 25 per cent. lymphocytes, 5 per cent. monocytes, and 1 per cent. eosinophils, Erythrocyte sedimentation rate was: 1 mm. in fifteen minutes. 2 mm. in thirty minutes, 4 mm. in forty-five minutes, 5 mm. in sixty minutes. Her symptoms decreased with rest in bed, but other areas of pain and tenderness appeared from time to time. One such, in the upper portion of the left rectus abdominis, caused pain when the patient attempted to raise her head from the bed, and on palpation this muscle appeared to be in spasm. At other times she complained of pain in the left upper extremity

and in the left gluteal region. Sometimes these pains lasted only for an hour or two. By December 4 she was almost free of pain and was allowed out of bed.

Discussion

The syndrome under discussion appeared to be characterised by pain in various muscles, particularly the trapezius. In most cases the disease was confined to the muscles of the neck, the duration of symptoms was short, and the discomfort did not interfere with work or other activities. In certain individuals, however, the muscle pain was so severe as to cause considerable disability. There was little systemic disturbance, aside from headache, in about half of the cases.

The clinical features were unlike those of Bornholm disease, in which high fever, prostration, pleural and abdominal pain are so common. None of the patients observed in the present epidemic of myalgia suffered pleural pain. An additional difference was that the trapezius muscle was invariably involved in "stiff neck," whereas Sylvest[3] (1934) found it affected only five times in seventy-two patients suffering from Bornholm disease. In contrast to the absence of similarity between this disease and epidemic myalgia of the Bornholm type, "stiff neck," especially in severe cases, resembles the common sporadic disease of acute fibrositis, in which the presence of localised areas of muscle tenderness, tingling sensations in the extremities, and lack of systemic symptoms are characteristic. This similarity is emphasised because fibrositis commonly involves the trapezius muscle. Copeman[4] (1939) makes the following statement: "Fibrositis of the shoulder muscles, more especially the trapezius muscle, is probably the commonest rheumatic complaint met with in routine practice. . . . Diagnosis is easy. No organic signs of disease will be found. There will be pain of fairly sudden onset in one or both shoulders, often shooting up the neck or even down the arms, simulating perhaps brachial neuritis."

Acute fibrositis is not usually considered to be epidemic in nature, but further observations are desirable to determine whether such cases are always sporadic or may sometimes be associated with other similar cases, or with cases of "stiff neck." It is probable that epidemics of the latter are not uncommon, but that since most affected persons are able to continue with

their routine activities and only the small number with severe or more generalised muscle pain come to the attention of physicians, epidemics cannot be detected without specific surveys.

Summary

1. A survey covering a period of two months was made to determine the incidence of "stiff neck" among a group of one hundred and sixty-three factory workers. Twenty-nine cases were discovered, an attack rate of 17·8 per cent.

2. The attack rate was higher in women, most of whom were in their third decade, than in men, most of whom were in their fifth decade.

3. Although the disease was usually mild, some persons were incapacitated for two weeks or longer.

4. The clinical features were unlike those of Bornholm disease but resembled those of acute fibrositis.

5. The purpose of the present communication is to direct attention to the occurrence of this syndrome in epidemic form.

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THE WELTMANN COAGULATION REACTION AND THE SEDIMENTATION TEST IN ARTHRITIS*

By DAVID H. KLING†

Two simple non-specific laboratory procedures are recognised to be of value in arthritis. One is the filament-non-filament leucocyte count (Eaton,[1] Steinberg,[2] Rawls[3]). Steinbrocker and Hartung[4] have found the non-filament count to be increased in

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almost 100 per cent. of cases of rheumatoid arthritis. However, the significance of this finding is diminished by the fact that the percentage of non-filament granulocytes was elevated also in almost half of the cases of osteo-arthritis. Increase of the total leucocyte count or of the non-filament percentage indicates the systemic reaction to inflammation or infection. The second test is the sedimentation reaction. Since Dawson and his co-workers[5] have stressed the importance of the sedimentation rate, it has become in the United States the most generally used test for the differential diagnosis between rheumatoid and osteo-arthritis, for prognosis and evaluation of the effect of therapy. The mechanism of the sedimentation reaction is complex. However, the quantity and intensity of protein breakdown by a pathological process and the subsequent disturbance of the equilibrium of the plasma play important rôles.

In 1930 Weltmann[6] described a third non-specific test based on the observation that diluted serum requires different amounts of bivalent electrolytes for heat coagulation according to the pathological process involved. To sera from exudative processes, higher concentrations of calcium chloride must be added than to normal sera in order to produce coagulation. On the other hand, sera from cases where fibrotic processes and liver damage are prominent require less calcium chloride. For the last five years this test was extensively investigated in Europe, and its usefulness for diagnosis and prognosis in various conditions confirmed. In the United States only Kraemer[7] and Levinson and his co-workers[8] have reported their observations of the test. Their conclusions support the European workers.

The mechanism of the Weltmann coagulation reaction is not entirely understood. Since the test is carried out on serum, it is not influenced by the fibrin content of the plasma. Carriere *et al.*[9] and Levinson *et al.*[10] have demonstrated that it is not dependent on the albumin-globulin ratio or total serum protein. Kretz and Kudlac[11] found that the concentration of calcium and chlorides in the serum does not influence the test. They assume that the reaction depends on qualitative changes in the serum proteins brought about by local tissue changes of either exudative or fibrotic nature. The filament-non-filament count, sedimentation test and Weltmann coagulation reaction reflect different systemic and local reactions and contribute to a more comprehensive understanding of the pathological physiology.

For this reason it appeared of interest to investigate the Weltmann reaction in various types of arthritis. Rheumatoid arthritis is generally regarded as a systemic disease. In the active stages exudative processes are prevalent, manifested by frequent presence of effusions and peri-articular swellings with increased tissue fluid. Therefore, it could be assumed that rheumatoid arthritis would give coagulation reactions in the range of exudative diseases. On the other hand, osteo-arthritis is a degenerative disease and occurs in advanced age where fibrosis and cirrhotic processes are frequent, which should tend to shift the coagulation reaction within the range of the fibrotic zone.

Technique of Weltmann's Reaction

From a stock solution of 10 per cent. crystalline $CaCl_2.6H_2O$ ten dilutions are prepared ranging from 1: 1,000 to 0·1: 1,000. The integral between each solution is 0·1: 1,000. 4·9 ml. of solution is pipetted into each of ten test-tubes which are numbered corresponding to their concentration from one to ten and placed in a rack. Tube I contains the highest concentration of calcium chloride and is placed to the left. To each test-tube 0·1 ml. of clear non-hæmolysed serum is added. The tubes are shaken and heated in a boiling-water bath for 15 minutes. The contents of the tubes after heating may remain clear, or show various degrees of turbidity or flocculation. The number of the test-tube showing flocculation is read and gives the coagulation band. In normal sera flocculation occurs in Tubes VI or VII corresponding to 0·5 to 0·4/1,000 calcium chloride. If flocculation occurs only in the Tubes I to V it is designated as a short band, shift to the left or exudative zone. If flocculation extends to Tube VIII and further, this reaction is known as a long band, shift to the right or the fibrotic zone. This technique is cumbersome and requires a large amount of fresh solutions, glassware and labour which impedes its general use.

A simple modification was described elsewhere[12] which permits carrying out the entire procedure with only one test-tube, one standard solution of calcium chloride and 0·1 ml. of serum. The technique of this modification is as follows:

Into a medium-sized test-tube (about $6 \times 0{\cdot}5$ inches) place 4·9 ml. of distilled water and 0·1 ml. of clear non-hæmolytic serum. Add from 0·1 ml. pipette 0·05 ml. of 1 per cent. calcium chloride (equal to 0·5 mgm.). Shake and bring to a boil over a

small flame. Cool and repeat the procedure until flocculation has taken place. Note the amount necessary to produce flocculation. Table I gives the conversion into the corresponding calcium chloride concentration and the number of the tube of Weltmann's original reaction. Violent boiling should be avoided because it may lead to foaming and loss of fluid. This is prevented conveniently by a finger cot, partially unrolled, slipped over the mouth of the test-tube. The observation for flocculation should be made after cooling.

TABLE I

Weltmann's Method:										
Tube	I	II	III	IV	V	VI	VII	VIII	IX	X
$CaCl_2$/1,000 ..	1·0	0·9	0·8	0·7	0·6	0·5	0·4	0·3	0·2	0·1
mgm. $CaCl_2$/5 ml.	5·0	4·5	4·0	3·5	3·0	2·5	2·0	1·5	1·0	0·5
Modification:										
ml. of 1% $CaCl_2$	0·5	0·45	0·4	0·35	0·3	0·25	0·2	0·15	0·1	0·05
		Exudative Zone Shift to Left Short Band				Normal Zone		Fibrotic Zone Shift to Right Long Band		

The sedimentation tests were carried out according to the Westergren method and read after one hour. Based on thousands of cases, we agree with the authors who have demonstrated that the simple Westergren method is more significant in arthritis than the various proposed modifications which only complicate the test and often confuse the results.

ANALYSIS OF MATERIAL

In this paper a comparative study of the Weltmann reaction and the sedimentation test in 250 cases of arthritis is presented. Ninety-eight cases were rheumatoid (infectious) arthritis, 88 cases were osteo-arthritis and 64 were miscellaneous types of arthritis.

Rheumatoid (*Infectious*) *Arthritis.*—Table II gives a detailed analysis of the values of coagulation reaction and sedimentation rates. Table III classifies the material in groups according to the outcome of both tests. In this and following tables the normal coagulation band is one where flocculation takes place up to Tube VI or VII (0·5 to 0·4/1,000 $CaCl_2$). A slightly short coagulation band is one where flocculation occurs only up to Tube V (0·6/1,000). A markedly short coagulation band is one where flocculation occurs up to Tube IV or less (0·7 to 1·1/1,000).

TABLE II.—COAGULATION BAND AND SEDIMENTATION RATE IN NINETY-EIGHT CASES OF RHEUMATOID (INFECTIOUS) ARTHRITIS.

Weltmann Reaction ($CaCl_2$ per ml.).	*Tube.*	*Per Cent.*	*Sedimentation.*	*Per Cent.*
0·3	VIII	4·1	0–10	10·2
0·4	VII	6·1	11–20	8·2
0·5	VI	18·4	21–30	28·6
0·6	V	18·4	31–40	16·3
0·7	IV	27·6	41–50	16·3
0·8	III	10·2	51–60	14·3
0·9	II	9·1	61–70	2·0
1·0	I	2·0	71–80	—
1·1		4·1	81–105	6·1
Total		100·0		100·0

A normal sedimentation rate is a drop of erythrocytes of 1 to 10 mm./hour, a slightly increased rate is from 11 to 20 mm./hour, a markedly increased rate from 21 to 105 mm./hour. Normal coagulation reaction occurred in 24·5 per cent. against a normal sedimentation in only 10·2 per cent. In 18 per cent. the coagulation was only slightly short and the sedimentation rate was slightly increased in 8·2 per cent. The coagulation band was markedly short in 53 per cent. and sedimentation rate was markedly increased in 81·6 per cent. The exudative process in rheumatoid arthritis is not pronounced enough in about half the

TABLE III.—SUMMARY OF COAGULATION BAND AND SEDIMENTATION RATE IN RHEUMATOID (INFECTIOUS) ARTHRITIS.

Coagulation Band.	*Per Cent.*	*Sedimentation.*	*Per Cent.*
Longer	4·1	—	—
Normal	24·5	Normal	10·2
Slightly short	18·4	Slightly increased	8·2
Markedly short	53·0	Markedly increased	81·6

cases to give a marked shift to the left. The coagulation band is therefore inferior as an indicator of rheumatoid arthritis to the sedimentation rate. On the other hand, we found in 4·1 per cent. a longer coagulation band than normal. It is possible that fibrotic changes had taken place either due to some phase of rheumatoid arthritis or to intercurrent diseases such as parenchymatous degeneration of liver or fibrotic tuberculosis. In 43 cases the reliability of both tests was gauged by the clinical course during long observation. The sedimentation gave a correct expression in 41 cases or 95 per cent., while the coagulation band did so only in 34 cases or 79 per cent.

While the sedimentation test is superior as a general indicator of the severity, course and therapeutic effect, yet in some cases the coagulation reaction may uncover important complications, and reflect more accurately the progress of the arthritis. The following case histories are given as illustrations.

Case 1.—S. B., white, female, aged fifty-two. Suffered from pain, swelling, stiffness and limitation of motion in numerous joints. When first seen, the left knee especially was involved and effusion and flexion contracture were present. There were periarticular swellings of the first phalangeal joints, and of the wrists and elbow joints. Rheumatoid arthritis was diagnosed. The sedimentation rate was 100 and the coagulation band was long—0·3/1,000 $CaCl_2$—indicating a fibrotic process. A check-up of the history revealed recurrent pleurisy fifteen and twenty years previously, and the examination showed old fibrotic tuberculosis with pleural adhesions. The influence of the fibrotic changes on the electrolytic threshold is evidently greater than of the exudative changes of rheumatoid arthritis.

Case 2.—H. B., white, male, aged forty-five. Suffered four years from pain and swelling of ankles, feet, knees, wrists, elbows and spine. Examination showed periarticular swelling of these joints and effusion in the right knee. X rays showed narrowing of the joint spaces and erosions of the articular surfaces of the wrists, elbows and knee joints. A diagnosis of rheumatoid arthritis was made. The sedimentation was 110 mm./hour. The coagulation band, however, was normal—0·4:1,000 $CaCl_2$. Further examination showed an old scar over the left ankle from a healed-up sinus during youth (probably tuberculous), scars in the cornea and an old fibrotic tuberculosis of the lungs. He also had a cholecystectomy two years before because of cholecystitis and stones. These fibrotic and cirrhotic changes explain the normal coagulation band in the face of an active rheumatoid arthritis. This case reacted poorly to treatment, and was still at the same level of activity after four years' observation.

Osteo-Arthritis.—Tables IV and V show a detailed analysis and summary of the results in 88 cases. Contrary to expectation,

Table IV.—Coagulation Band and Sedimentation Rate in Eighty-Eight Cases of Osteo-Arthritis.

Weltmann Reaction ($CaCl_2$ per ml.).	*Tube.*	*Per Cent.*	*Sedimentation.*	*Per Cent.*
0·3	VIII	4·5	0–10	69·8
0·4	VII	28·5	11–20	15·2
0·5	VI	27·3	21–30	5·6
0·6	V	30·7	31–40	5·6
0·7	IV	4·5	41–50	—
0·8	III	1·2	51–60	1·9
0·9	II	3·4	61–70	1·9
1·0	I	—	—	—
1·1		—	—	—
Total		100·0		100·0

TABLE V.—SUMMARY OF COAGULATION BAND AND SEDIMENTATION RATE IN OSTEO-ARTHRITIS.

Coagulation.	*Per Cent.*	*Sedimentation.*	*Per Cent.*
Longer	4·5	—	—
Normal	55·7	Normal	69·8
Slightly short	30·7	Slightly increased	15·1
Markedly short	9·1	Markedly increased	15·1

long coagulation bands were found only in 4·5 per cent., a fraction of one per cent. higher than in rheumatoid arthritis. Normal coagulation bands were found in 55·7 per cent., while the sedimentation rate was normal in almost 70 per cent. The percentage of slightly short coagulation bands was 30·7 and of markedly short bands 9·1 per cent. The sedimentation rate was slightly increased in 15 per cent. and markedly in 15 per cent. A group of 14 cases was followed clinically for a long period to check on the relative correctness of both tests. It was found that sedimentation was correct in 9 cases (92·7 per cent.), while the coagulation band was correct in 5 cases (63·5 per cent.). Therefore, also in osteo-arthritis the sedimentation rate is more significant than the coagulation band. Only in a small percentage is the degenerative character of osteo-arthritis reflected by the shift of the coagulation band into the fibrotic zone. As in rheumatoid arthritis, the test is useful in discovering intercurrent complications as illustrated by the following case history:

CASE 3.—C. C., white, female, aged fifty-six. For two years she had pain and swelling of the phalangeal joints and a trigger finger of the fourth right finger following a sprain. The examination revealed changes in the fingers characteristic of Heberden's nodes. There was also periarticular swelling of the first phalangeal joint of the left fourth finger. The clinical diagnosis was a mixed type of arthritis. Sedimentation rate was 15 mm. and the coagulation band was considerably shortened (0·7/1,000 $CaCl_2$). After a period of observation of four months and following an attack of influenza, fever, cough, night sweats, and loss of weight appeared. A check-up showed an exudative tuberculosis with infiltration of both apices. Intradermal tuberculin test was positive in a dilution of 1 : 1,000,000. On check-up sedimentation rate was 35 mm. In this case the coagulation band indicated the presence of an exudative condition sooner and more definitely than the sedimentation rate.

MISCELLANEOUS CASES

1. *Gout.*—Of 9 cases, examined during attacks, the sedimentation rate was slightly increased in 3 and markedly increased in 6. The coagulation band was longer in 1, normal in 5 cases, slightly

shorter in 2 and markedly shorter in 1. Gout, although regarded generally as a metabolic disease, shows usually during acute attacks an increase in sedimentation rate. This is perhaps explained by marked inflammatory changes in the joints characteristic of the acute phase. The coagulation band was shorter only in one-third of the cases. It returned to normal when the sedimentation was still elevated. In gout degenerative changes of liver, kidney, myocardium and blood vessels are frequent. This may counteract the tendency toward shortening of the coagulation reaction by inflammatory joint changes. While in rheumatoid arthritis the coagulation reaction was markedly shorter in 53 per cent., in gout it was so only in 11·1 per cent. Therefore, in atypical cases, which resemble rheumatoid arthritis and have a normal or long coagulation band in the presence of a high sedimentation rate, the possibility of gout should be investigated.

2. *Gonorrhœal Arthritis.*—Out of 9 cases, 3 gave a normal sedimentation, 2 gave a slightly increased and 3 a markedly increased sedimentation. Two gave a normal Weltmann reaction, 2 a slightly shorter and 3 cases a markedly shortened Weltmann band (0·7 to 1·0/1,000 $CaCl_2$). Two cases gave a longer coagulation band (0·3 and 0·4/1,000 $CaCl_2$). Both the sedimentation test and the Weltmann reaction showed characteristic changes in the acute exudative stage and tendency to become normal when the response to treatment was favourable. The transition from a shorter to a longer band after the subsidence of the symptoms led to the discovery of an incipient liver cirrhosis in the following case:

Case 4.—J. G., white, male, aged forty-seven. The patient contracted gonorrhœa three months before examination, followed by pains and swelling of knees and hands. Examination revealed periarticular swelling and tenosynovitis of the metacarpo-phalangeal joint of the right index finger, swelling and effusion of the right knee joint and tenderness over both hips. Sedimentation was 50 mm. and the coagulation reaction was 0·6/1,000 $CaCl_2$. The gonococcus complement-fixation test was strongly positive. Under fever therapy there was a gradual recession of symptoms, the sedimentation dropped to 32, and the coagulation reaction became normal (0·5/1,000 $CaCl_2$). One month later, the symptoms having subsided almost completely, sedimentation was normal (10 mm.) and coagulation band short (0·2/1,000 $CaCl_2$). Examination revealed cirrhosis of the liver, chronic myocarditis and arterio-sclerosis.

3. *Tuberculous Arthritis.*—Of 4 cases sedimentation was normal in 1 case, slightly increased in 1, markedly increased in

2 (up to 105 mm.). The Weltmann band was normal in 2, markedly short in 1 and long in 1.

4. *Traumatic Arthritis.*—Of 7 cases sedimentation was normal in 5 cases, slightly increased in 1, markedly increased in 1. Coagulation bands were normal in 5 cases, slightly short in 2 cases in which signs of secondary inflammation were present clinically.

5. *Sacro-Iliac Arthritis.*—Of 11 cases, not definitely classified, the sedimentation was normal in 4, slightly increased in 4, and markedly increased in 3 cases. The coagulation band was normal in 7 cases and slightly short in 4. In this group the sedimentation rate indicated more frequently inflammatory changes than the coagulation reaction.

6. *Myositis.*—Of 8 cases sedimentation was normal in 5, markedly increased in 2 cases, slightly increased in 1 case. Coagulation bands were normal in 5 cases, slightly short in 1 and long in 2 cases.

7. *Neuritis.*—Of 3 cases sedimentation rate was normal in 2 and slightly increased in 1. The coagulation band was normal in all 3 cases.

8. *Tenosynovitis.*—Of 6 cases sedimentation was normal in 3 cases, slightly increased in 2 and markedly increased in 1. Coagulation was normal in 3 cases, short in 2 and long in 1.

9. *Arthralgia.*—In 2 cases of subjective pain in the joints with no objective symptoms sedimentation rates and coagulation bands were normal. Such cases present a difficult problem because of the possibility of an incipient rheumatoid arthritis which did not as yet advance to objective symptoms. Corroborative laboratory evidence is therefore important.

10. *Ankylosing Spondylitis* (*Strumpell-Marie Type*).—Of 3 cases 1 showed high sedimentation rate of 110 mm. and a short coagulation band (0·8/1,000 $CaCl_2$). One case which still showed some activity had a sedimentation of 4 mm., but a short coagulation band (0·7/1,000 $CaCl_2$). In the third case, which had been quiescent for a long period, sedimentation was 40 mm. and coagulation was normal.

11. *Recurrent Rheumatic Fever.*—In 2 cases of recurrent attacks of rheumatic fever and arthritis in adults the first case showed sedimentation of 38 and short coagulation band (0·7/1,000 $CaCl_2$); the other case came under observation at the beginning of a recurrence and is reported below:

CASE 5.—The patient was white, male, aged thirty-six. He had pain in joints in childhood for only one day. At the age of seventeen numerous joints were involved, but chiefly ankles, the right knee and the fingers. This attack lasted six to seven months. At twenty-eight years of age he had acute swelling of the left knee joint and was in bed for one month. At the time of examination he had indefinite pain in the knees and the toes, but no objective swelling or limitation of motion. The heart showed a compensated mitral stenosis and insufficiency. Sedimentation was 5 mm., but coagulation was short (0·6/1,000 $CaCl_2$). Within the next three weeks effusions developed in both knees, left ankle and wrists, and tenderness in the spine. Sedimentation increased to 30 mm. In this case the coagulation indicated a recurrence of rheumatic fever before the clinical symptoms and while the sedimentation rate was still normal.

SUMMARY AND CONCLUSIONS

The analysis of 250 cases leads to the conclusion that the Weltmann coagulation reaction in arthritis does not possess the general utility of the sedimentation test. In rheumatoid arthritis the coagulation reaction was in the exudative range in 71 per cent., but in only 53 per cent. the coagulation band was markedly shorter. In osteo-arthritis only 5 per cent. of the cases fall in the fibrotic range. Neither exudation nor fibrosis is pronounced enough in these groups of arthritis to give a clear-cut line of cleavage. Also as a check on the clinical course and effect of treatment the sedimentation test is superior to the coagulation reaction. On the other hand, in both groups there were cases where the coagulation band was more accurate or led to the discovery of concurrent exudative or fibrotic processes not revealed by the sedimentation test. In the group of miscellaneous types of arthritis these general conclusions are borne out. A high sedimentation rate and normal or longer coagulation band may be valuable for detection of atypical gout. This observation, however, requires confirmation in a larger material.

The coagulation band in arthritis cannot and should not substitute the sedimentation test as a diagnostic or prognostic procedure. It may, however, be carried out together with the sedimentation test and the filament-non-filament count as the third important non-specific test. Each of these tests reflects a different segment of systemic or local manifestations of disease which supplement each other. The combination of the three tests permits a more balanced estimation of the underlying pathological physiology. The described modification renders the technique of the coagulation reaction just as simple as of the other two tests.

A SPECIFIC REACTION IN ACUTE RHEUMATISM AND RHEUMATOID ARTHRITIS

By A. J. MESTER

The need for an objective sign or test for the existence or non-existence of rheumatic infection of joints is of great importance. Researches to this end have been carried out during a period of several years in the First Medical Clinic, Jagellons University, Cracow, Poland. Injection of many different substances—histamine, pilocarpine, atropine, adrenaline, milk, etc. — intracutaneously, subcutaneously and intravenously, were tested by many methods but no specific reaction was identified. Search was made for " H " substances released by strictly regulated skin trauma, but no obvious specific reaction could be detected. Blood was taken from rheumatic and non-rheumatic patients before and after fixed skin trauma. At the height of Lewis's triple response blood was taken from the vein and both injected intramuscularly on the next day—Si, without H substance and Sii containing H substance. All the patients were in bed and fasting, and examinations were made for general, local, and blood reactions. It was found that rheumatic patients had a greater production of H substances than the control patients, but thyro-toxic and neurotic patients revealed also an increased production of H substances.

After prolonged investigations a reaction, however, was found which proved to have a high specificity for rheumatism. This reaction depends on the special sensitivity of rheumatic patients to salicylic acid.

The patients are kept in bed preferably, but ambulatory patients may be examined in the sitting position; in either case they must be fasting. A count is made of the white blood corpuscles, and after this count 1 cubic centimetre of a 0·1 per cent. aqueous solution of salicylic acid is injected intradermally, forming five blebs each of 0·2 c.cm. on the flexor aspect of the forearm, and after thirty minutes another white count is made. During this time the patient is forbidden to eat, drink, or make any effort. Nearly all rheumatic patients, acute, subacute or chronic, show after the injection a drop in the number of white cells after thirty minutes; in a further group a second count was made after sixty minutes, but only a small number of rheumatic patients

showed a drop in the white count after this interval, and these were generally cases in which the infection was of long standing. The lowest figure regarded as positive was 15 per cent. below the level before injection, but diminutions as great as 50 to 70 per cent. were observed. This reaction appears to be positive in every kind of rheumatic infection not only of joints but also of heart, serous membranes, nerves, eyes, etc. In a series of tests 98 per cent. of rheumatic patients gave a positive result, while all controls were negative.

Two cases may be described to demonstrate the value of the reaction. A young woman of 32 years was admitted to the clinic with high temperature, severe arthritis and tachycardia; the spleen was not palpable and only slightly enlarged to percussion, the urine showed a trace of albumin. The electrocardiogram showed a simple tachycardia. The diagnosis lay between acute rheumatic fever and sepsis with joint metastases. The sedimentation rate was over 100 mm. 1 hr. Westergren; there was a leucocytosis between 15,000 and 18,000 per cu. mm. and a shift to the left in the Schilling-Arneth count. Blood cultures proved sterile. The salicylic test was negative. Careful search was made for any septic focus without success. At the post mortem ulcerative endocarditis was found, and was evidently the origin of a general septicæmia with joint metastases.

A second case, a woman of 44 years, was admitted with general chronic joint changes of over two years' duration, effusion in both knees and swelling, and deformity of many joints both large and small. The heart and lungs were normal. There was albuminuria 10 to 20 per cent., with hyaline casts, but no lipoids or red-blood cells. The blood pressure was low, spleen and lymph glands enlarged. Tests for syphilis in blood and cerebro-spinal fluid were negative. The salicylic reaction was strongly positive. Rheumatoid arthritis with generalised amyloidosis was diagnosed and the post-mortem examination confirmed this; no suppurative process, tuberculosis nor syphilis was discovered. The amyloid degeneration appeared to be solely due to the chronic rheumatic infection.

The test is obviously of service in detecting malingering since rheumatic pains may be complained of and be impossible to disprove by ordinary methods, but the diagnosis must always be relied upon only in conjunction with clinical examination as is the case with all biological tests. For example, a syphilitic patient

may show joint pains which may be syphilitic or rheumatic, and the test will determine which; the same applies in tuberculosis. The test has been used in several Polish hospitals and found of great service. Professor Lenoch, in the Internal Clinic in Prague, used the test in a hundred and forty cases, and came to the conclusion that it was of great diagnostic value and highly specific.

The salicylic reaction is also of great theoretical importance. It is positive in acute and subacute rheumatic fever and in chronic rheumatoid arthritis. Until now the question of the relationship between rheumatic fever and rheumatoid arthritis has remained open. Some authors are of the opinion that these two diseases are two aspects of the same disease, others think they are two distinct entities. The author is convinced of the relationship between the two and that the link is the "rhumatisme fibreux" of Jaccoud, which is not infrequently met with in France, Poland and Austria.

The immuno-biological skin reactions with streptococcus extracts are in both diseases in the same proportion, positive. The most characteristic product of rheumatic inflammation, the nodules met with in acute and subacute rheumatism, are of the same histological structure as the rheumatic nodules so often seen in rheumatoid arthritis, which are often overlooked because a sufficiently careful search has not been made. The blood findings are also almost identical.

Another problem is the relation between rheumatoid and osteo-arthritis. While peripheral blood and the bone marrow picture in rheumatoid arthritis is inflammatory, osteo-arthritis does not show any blood changes in either the peripheral circulation or the bone marrow. In rheumatoid arthritis the myelogram shows an increased number of plasma cells, reticulum cells and eosinophils, mature and immature, while in osteo-arthritis these cells are normal in number. In osteo-arthritis there is no infective factor, and the author would suggest that a better name would be joint sclerosis in analogy to arterio-sclerosis.

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FRACTURES IN CHRONIC ARTHRITIS*

By GEORGE J. BAER†

The incidence of fractures in chronic arthritis, the rate of healing, and the complications following fractures have not been recorded in modern medical literature. A review of the literature from 1900 to 1940 makes no mention of this subject. The 1,625 case records of arthritis at the Robert Breck Brigham Hospital were reviewed to determine the frequency of fractures, the rate of healing, the ætiology, and the effect upon the systemic and local disease processes. The case records examined included the different types of disease in all accepted classifications.

Fractures are among the less common complications of arthritis. They occurred 21 times, or in 1·2 per cent. of the cases examined. Dislocations, on the other hand, are common.

It is frequently difficult to differentiate a fracture from "disintegration" at the bone ends due to atrophy and cystic degeneration. In the roentgenogram one frequently can see a fracture line at the bone ends where disintegration has taken place. Should such disintegrations be considered as fractures, the incidence of fractures in chronic arthritis would be increased statistically. Such "infractions," as they have been described by Knaggs,[1] have not been classified as fractures in this survey. A fracture to be so classified had to satisfy the criteria commonly accepted by all surgical textbooks.

From a theoretical point of view one would expect fractures to be common in patients with rheumatoid arthritis. The marked bone atrophy with loss of lime salts, cystic degeneration of bone, and loss of muscle tone would lead one to such a conclusion. However, these patients, because of the loss of joint function, pain, and muscular weakness, lead a rather guarded existence, so that the forces necessary to produce a fracture are infrequently encountered. In rheumatoid arthritis the simplest type of trauma is sufficient to produce a fracture. Weight-bearing alone was the only force necessary in one instance, and muscular effort in another. In no case was major trauma the cause of a fracture except during manipulation of a joint under

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anæsthesia. The recognised pathology of bone in osteo-arthritis would lead one to conclude that the incidence of fractures would be within the limits of statistical expectancy following major trauma in normal bone. More violent trauma accounted for the fractures in this latter group.

In 21 cases of fractures, 14 of them occurred in rheumatoid arthritis. There were 8 females and 6 males (Table I). The majority of the patients were in middle life. The youngest was 13 years and the oldest 72 years. The average duration of the disease before a fracture was sustained was 11·4 years. The femur was involved 9 times (neck of femur once); humerus 3 times; tibia twice; vertebra, fibula, radius, and ulnar styloid each once. A simple shaft fracture was most frequent, occurring 9 times; comminuted fractures of the shaft twice; impacted fractures at the bone ends and of the vertebra 3 times; and greenstick fracture once.

TABLE I.—RHEUMATOID ARTHRITIS

Case.	*Sex.*	*Age.*	*Duration of Disease.*	*Bone Involved.*	*Type of Fracture.*	*Union.*
332 ..	F.	21	18 years	Left femur, shaft	Comminuted	Yes.
5,642 ..	F.	57	15 months	Left humerus, shaft	Simple	Yes.
1,492 ..	M.	31	10 years	Vertebra	Impacted	Yes.
594 ..	M.	43	11 years	Right femur, shaft	Simple	Yes, delayed.
1,538 ..	M.	35	11 years	Left femur, shaft	Simple	Yes.
596 ..	F.	13	10 years	Left femur, left tibia	Simple	Yes.
1,298 ..	M.	56	14 years	Left femur	Impacted	Yes.
571 ..	M.	52	4 years	Left humerus	Simple	Yes.
2,839 ..	F.	72	1 year (?)	Radius and ulnar styloid	Simple	Yes.
4,960 ..	F.	59	24 years	Tibia and fibula	Simple	Yes.
1,137 ..	M.	22	8 years	Right femur	Simple	Yes.
393 ..	F.	38	5 years	Both femora	Simple	Yes.
2,326 ..	F.	56	26 years	Neck femur	Simple	Yes.
65 ..	F.	49	18 years	Humerus	Simple	Yes.

Surgical manipulation of a joint under anæsthesia was responsible for 5 fractures. The remainder were the result of simple trauma.

In each instance there was atrophy of the fractured bone. The bone atrophy was minimal in 4 cases and marked in 10 cases.

The degree of bone atrophy did not correspond to the duration of the disease, since some of the early cases had more marked atrophy than those of long duration. Following the healing of a fracture the bone atrophy persisted in all parts of the bone except about the fracture site, where the newly calcified callus was conspicuous by its density. Union took place in all cases, and proceeded normally except in one case—a fracture of the mid-shaft of the femur—where union was delayed.

In the case of a fracture in a limb where a joint or joints had been involved by rheumatoid arthritis, immobilisation of the limb in a plaster cast did not promote ankylosis or permanently decrease the range of joint motion. After the cast was removed some limitation of motion in the affected joints was noted, but with physical therapeutic measures the range of motion that was present before the fracture occurred was soon regained.

In 8 cases the sedimentation rate was elevated at the time the fractures were sustained. The arthritis was considered active in these cases. The fact that a fracture occurred did not alter the course of the active arthritis, nor was there a generalised or localised exacerbation in the quiescent cases.

One fracture was found in a patient with gonococcal arthritis. The disease had been present six weeks and was subsiding when a Colles fracture resulted from a fall upon the outstretched arm with the wrist dorsiflexed. The wrist joint had been involved in the generalised gonococcal arthritis. There was slight bone atrophy. Healing took place in six weeks.

TABLE II.—OSTEO-ARTHRITIS

Case.	*Sex.*	*Age.*	*Bone Involved.*	*Type of Fracture.*	*Union.*
1,982 ..	M.	65	Ribs	Simple	Yes.
1,738 ..	M.	66	Ribs, vertebra	Simple Compression	Yes.
5,639 ..	F.	75	Neck of femur	Simple	Yes.
536 ..	F.	57 (?)	Phalanx of toe	Simple	Yes.
1,220 ..	F.	64	Vertebra-rib	Compression	Yes.
3,730 ..	F.	56	Both radii, left ulna, vertebra	Simple	Yes.

The 6 cases of osteo-arthritis included 4 females and 2 males (Table II). These patients were in or past the sixth decade of life. The youngest was 56 years and the oldest 75. The vertebræ were involved 3 times; the ribs 3 times; radius twice; neck of

femur, phalanx of toe, and ulna each once. A simple fracture of the shaft occurred in all the long bones except for the neck fracture of the femur. The vertebral fractures were of the compression type. Major trauma accounted for 5 fractures and muscular effort (ribs) for 1. Firm union took place in all cases in normal time. Atrophy of the fractured bones was not noted in 4 cases and was minimal in 2.

The sedimentation rate was elevated in 2 cases and was not determined in the others. Fractures did not alter the arthritic process.

All the fractures in this survey were reduced and treated by well-recognised and accepted methods.

Since this material has been compiled three fractures in patients with rheumatoid arthritis have been observed within one month. All of them are now under treatment, and the fractures are healing normally as revealed by roentgenograms. Simple trauma produced these fractures in atrophic bones.

It must be emphasised that when a fracture occurs in a limb with involved joints, immobilisation in a plaster cast is justified only long enough to allow sufficient callus to form to hold the fragments in good alignment. The cast must then be removed and the limb immobilised in a splint so arranged that passive motion of the affected joint can be easily accomplished to prevent ankylosis or marked limitation of motion.

It is obvious that fractures in osteo-arthritis are more common than this survey indicates. Only those patients with osteo-arthritis whose disease was symptomatic gained admission to the hospital. In a large series of fractures the incidence of fracture in patients with concomitant osteo-arthritis would be much higher than among a group of symptomatic osteo-arthritic patients. It is likely that fractures in rheumatoid arthritis are more common than the figures here presented would indicate. Once the possibility is recognised and a more careful search made for fractures, future surveys should reveal a higher percentage of cases.

Summary

From this survey one may conclude that fractures are among the less frequent complications of chronic arthritis. Healing takes place normally and a firm union can be expected. A fracture has no bearing on the active disease process *per se*, nor will it

promote an exacerbation of a quiescent arthritis. Simple trauma is sufficient to fracture the atrophied bones of the rheumatoid patient. Limitation of motion or ankylosis of joints need not occur if proper precautions are used. In osteo-arthritis fractures are usually produced by major trauma that would be sufficient to produce a fracture in normal bone.

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GOUT AND MALE PSEUDOHERMAPHRODISM: REPORT OF A CASE*

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THE curious fact that gout occurs predominantly among men was known to Hippocrates, and records indicate that throughout the twenty-four centuries that have elapsed since his time, women have for the most part continued to escape this painful malady. In the twenty-ninth aphorism of Hippocrates, according to Adams, it was stated that "a woman does not take the gout unless her menses be stopped," and in 1851 Gairdner wrote in a textbook on gout that ". . . women, though not wholly exempted from attacks of gout, do, notwithstanding, enjoy a greater comparative immunity." Similar observations have been made by many others since Gairdner's time. Practically every modern American authority on gout has observed that there is a predominance of the disease among men, although the exact ratio has varied in different reports. In a series of thirty-six cases reported by Futcher in 1902, all the patients were men, and Hench[6,7,8] has repeatedly stated that 98 per cent. of patients who have gout are men. Other American series in which a predominance of the disease among men is noted include those of Williamson (116 cases, one female), Schnitker and Richter (fifty-five cases, four females), Kinell and Haden (135 cases, five women) and Cohen (forty-seven cases, three women). In England, France

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and Germany gout also seems to occur mostly among men.[11, 12] Thus, many statistics tend to bear out the warning of Hench[6, 7, 8] that a diagnosis of gout must be made for a woman only with caution, and that such a diagnosis must be based on the same requirements as would apply if the diagnosis were being made for a man.

Female immunity to gout is unexplained. It was attributed by Hippocrates to the " purifying " effect of the menses, and by Gairdner to the greater " purity and propriety " of women's lives. To this day, no better explanations than these are available, however unsatisfactory they may be.

Men deprived of their gonads have been thought to share the immunity of women to gout. At least, in Hippocrates' day, it was said that eunuchs " did not take the gout nor become bald."[1] About six hundred years later, Galen spoke of this apparent immunity of eunuchs to gout as resulting from a change to a cold temperament like that of women. He noted, however, that those eunuchs who fell into " sloth and intemperance " were likely to acquire the disease.

Nowhere in medical literature have I encountered a case resembling that of this report, a case in which a patient had both the developmental fault of male pseudohermaphrodism and the metabolic fault of gout.

REPORT OF A CASE

The patient, fifty-five years old, came to the Mayo Clinic in April of 1939, complaining of recurring attacks of painful swelling affecting the " bunion joints." A diagnosis of gout had been made by the patient's physician at home. There was no familial history of gout, but the history in other respects was of interest. The patient, an Egyptian, had always been aware that her genitalia were abnormal. (I shall refer to this patient as a " female " because she had always looked on herself as being a woman.) She had never menstruated, and had not married, but had always dressed in women's clothes and had worn her hair long. She had been forced of necessity to wear men's shoes because of her large feet.

She had been obese even during childhood, and at the age of fifteen years weighed 226 pounds (102·7 kg.). She weighed 232 pounds (105·4 kg.) on admission to the clinic. A friend described the patient as " an excellent cook." She had always eaten heartily, had taken meat once or twice daily, and often had entertained her friends with huge meals, the main course of which consisted of chicken, turkey, lamb and

other meats, all cooked in butter and served with rice, beans and nuts. For twenty years she had been accustomed to take large quantities of alcoholic liquors, and often had taken a pint of whisky daily.

At the age of thirty-five years, twenty years before her visit to the clinic, she had suddenly been afflicted by swelling with severe throbbing pain in the region of the attachment of the right Achilles tendon. This attack lasted two weeks and then the condition of the foot returned to normal. Her physician at home had made a diagnosis of gout during this attack and had treated the foot with applications of heat, but had suggested no further treatment.

One year later, a similar acute attack of violent pain and swelling had developed in the region of the right big toe, and had persisted for ten days, after which the foot again returned to normal. Since that time she had experienced similar episodes once or twice yearly; the region of one or the other " bunion joint " was affected, and the attacks lasted for from three or four days to ten days in some attacks. Such attacks often followed a day of excessive eating and drinking, and seemed to have no definite seasonal incidence. The longest interval which had elapsed between attacks was eighteen months; the shortest was four months. Usually the attacks appeared suddenly over the course of two or three hours, caused throbbing, intense pain which was equally severe day and night, and which was associated with swelling and redness over the joint involved. Usually, severe sensitiveness was present which made it impossible for the patient to keep the foot covered because even the weight of bed-clothes was too much for her to bear. Fever did not accompany the attacks, and the attacks always disappeared, leaving the feet painless. The most recent attack had appeared in the right " bunion joint " ten days before the patient had come to the clinic.

She never had experienced renal colic and had had no attacks of olecranon bursitis. One year before coming to the clinic her physician at home had discovered albumin in the urine.

Examination disclosed the patient to be obese, 5 feet 6½ inches (169 cm.) in height, heavily built, with broad shoulders and narrow hips. The voice was deep and of masculine timbre. There was a moderate amount of hair on the chin. The breasts were small, and the abdomen was obese and hung down over the pubes as an apron. The pubic hair had the feminine distribution. The labia majora were large and contained soft masses which felt like testes; the mass on the right was placed lower in the labium than that on the left. The clitoris was 2 inches (5 cm.) in length, flaccid and had a well-developed glans. There was no vagina; instead, there was merely a small invagination behind the urethra in the region of the introitus (Fig. 1). An attempt to palpate the pelvic organs by rectum was unsatisfactory because of the patient's obesity.

At the time of the first examination the patient's blood pressure was 215, systolic, and 110, diastolic, expressed in millimetres of mercury. At examination the subsequent day the blood pressure was 180, systolic, and 100, diastolic, expressed in millimetres of mercury. The right " bunion joint " was moderately swollen, red and markedly tender, particularly over the medial aspect. There were no subcutaneous tophi and no other joints were affected. Examination of the optic fundi showed sclerotic, narrowed retinal arterioles similar to the retinal arterioles in hypertension and dot-like regions about both

FIG. 1.

The clitoris is two inches in length and has a well-developed glans. Only a small pit behind the urethra marks the site of the vagina. No free vaginal canal is present.

maculæ which appeared to be the residual effects of previous " œdema exudates." A small region of hæmorrhage was noted below the left macula.

A single specimen of urine contained albumin (3 plus), with casts and occasional erythrocytes. Results of blood counts and estimation of hæmoglobin were normal and the result of a flocculation test for syphilis was negative. Values for uric acid were 5·1 mg. per 100 c.c. of whole blood (normal 2 to 2·5 mg.) and 7·9 mg. per 100 c.c. of serum (normal under 6 mg.). The value for urea in the blood was 46·0 mg.

per 100 c.c. (normal under 40 mg.), and the result of the urea clearance test was 27·3 c.c. (normal 40 c.c.) with a urine volume of 47 c.c. in one hour.

Roentgenograms of the right foot showed a spur to be present at the site of attachment of the Achilles tendon, on the posterior inferior aspect of the cuboid bone, and on the medial aspect of the distal phalanx of the great toe. These probably represented unrelated osteoarthritis. Slight roughening was noted on the medial side of the head of the first metatarsal bone (Fig. 2), suggestive of the presence of gouty tophi. Roentgenograms of the left foot demonstrated a more advanced

FIG. 2.—ROENTGENOGRAMS OF THE LEFT (*a*) AND RIGHT (*b*) FEET, SHOWING DESTRUCTIVE CHANGES ABOUT THE HEAD OF THE FIRST METATARSAL BONES CHARACTERISTIC OF OSSEOUS TOPHI.

The process is far more advanced in the right foot than it is in the left.

destructive change, characteristic of gouty tophi affecting the head of the first metatarsal bone.

A twenty-four-hour specimen of urine examined for androgens by the method of Drips and Osterberg gave a reaction equivalent to a concentration of 2 to 8 mg. of androsterone (usual findings for women, 1 to 4 mg.; for men, 2 to 8 mg.).

On the basis of the classic history of recurring acute attacks of arthritis affecting the feet, with complete remissions between these episodes, an elevated value for uric acid in the blood, and roentgenographic evidence very suggestive of gouty arthritis, the diagnosis of acute recurrent gouty arthritis was made.

Comment

This patient presented features of both sexes. She was like a male in that her shoulders were broad and her hips were narrow; the voice was coarse, a beard was present, the breasts were underdeveloped and the daily excretion of androgens was high. The patient resembled a woman in personality, in distribution of pubic hair and, to some extent, in the external appearance of the genitalia. The fact that gout developed would tend to suggest that constitutionally the patient was predominantly male.

Summary

A case is reported in which a patient with bisexual genitalia, male configuration of the body, but with a predominantly female personality, suffered from characteristic attacks of acute gouty arthritis and also severe hypertension.

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REVIEWS AND COMMENTARIES FROM CURRENT LITERATURE

The Action of Gold in the Treatment of Rheumatoid Arthritis.

Since Forestier first advocated the use of gold salts in the treatment of arthritis the method has rapidly grown in popularity until it has come to be regarded as the most promising method at present at our command, but a method attended with considerable risk of serious toxic effects. Reports from the clinical aspect have been numerous, but hitherto biochemical investigation has received but little attention, and the appearance of a series of articles bearing on this point deserves serious consideration.

R. H. Freyberg, Walter D. Block and S. Levey have published a preliminary report of their researches under the title "Metabolism, Toxicity and Manner of Action of Gold Compounds used in the Treatment of Arthritis" (*Journ. Clin. Inv.*, xx., 4, pp. 401-412). The fate of gold after injection, the tissues and tissue fluids affected, the route and speed of excretion, are chiefly dealt with in this report. They have used a photo-electric colorimetric micromethod specifically designed for this work by Block and Buchanan (*Journ. Biol. Chem.*, 1940, **136**, 379). The research was first directed to analysis of the blood, the urine, and the synovial fluid before and after the injection of gold salts in a series of cases of typical rheumatoid arthritis. The salts used were gold sodium thiomalate (myochrysine), gold sodium thiosulphate (*e.g.*, crisalbine, sanocrysin), and colloidal gold sulphide (aurol sulfide), the two former by the *intramuscular* route and the latter both intramuscularly and orally. The two former gave fairly uniform results, but those obtained by the use of colloidal gold were variable. The figures given throughout are the amounts of metallic gold and not of the gold salt employed.

Gold was found in the plasma in increasing amounts as the amount of gold injected increased; the course started usually with a small dose and gradually increased to 50 mg. of gold at weekly intervals. In a typical instance, after the first dose of 50 mg. given on the twenty-first day had been injected, the amount of gold in the plasma averaged about 0·8 mg., the daily values fluctuating somewhat, tending to increase after each

increase of dose; in this case the weekly dose was reduced to 25 mg. of gold, after which the average plasma content was lower and did not increase as more gold was administered.

The excretion of gold in the urine increased as larger amounts of gold were given, though the increase was not directly proportional. Excretion does not keep pace as the amount injected increases, and this retention is important. In one case when the dose of 50 mg. was reached on the twenty-first day an average of only 1 mg. was excreted daily during the week following before the next dose of 50 mg. was due on the twenty-eighth day; when the dose was reduced to 25 mg. excretion showed a definite diminution. After a course of 500 mg. in one case, the plasma contained gold for thirteen weeks after the last injection, and it was found in the urine for sixteen weeks; in other cases the urine contained gold seven, nine and ten months after the treatment ended. Fæcal analyses were done in some of the cases, and indicated that the urine was the chief route of excretion.

Five out of six cases who received large weekly doses of gold had significant toxic reactions, while none of the eight who received weekly doses of 25 mg. had any evident toxic reaction. Another type of reaction noted occasionally shortly after a dose of the drug, not necessarily a large one, was headache, flushing of the face, a sense of tightness in the throat and occasionally a purpuric dermatitis. This appeared to indicate sensitivity to gold, and when it occurs may be a warning of possibly serious effects if the treatment is continued.

When colloidal gold sulphide was used either orally or intramuscularly, the plasma and urine values varied greatly in different patients; some absorbed gold and had plasma and urinary values comparable to those obtained with the other salts studied, but most of the patients had very low plasma gold concentration and excreted little gold in the urine, even though the colloidal gold sulphide was given in amounts providing much more gold than was supplied in the crystalline forms.

Further investigations are being carried out in the endeavour to discover the tissues in which gold is deposited and also to determine, if possible, whether benefit depends upon the circulation of a certain minimal amount of gold for a minimal length of time.

Hartung, Cotter and Gannon report similar investigations which they have carried out (*Journ. Lab. and Clin. Med.*, xxvi.,

11, pp. 17-50). The method they used was that described by Pollard (1937) (*Analyst*, **62,** 597) and Jamieson and Watson (1938) (*Analyst*, **63,** 702) with some modifications. All the subjects were cases of rheumatoid arthritis, and observations were made during routine treatment with gold sodium thiomalate administered *subcutaneously*. The average dose varied from 25 mg. of gold sodium thiomalate once a week to 50 mg. every other day; results were recorded as metallic gold. In the case receiving 50 mg. of the salt (equivalent to 25 mg. gold) on alternate days, the daily excretion in the urine during the thirteen days of the observation reached a maximum of 12·83 mg.=9 per cent. roughly. The serum level during this time varied from 0·22 to 0·50 mg. per cent.; the synovial content was parallel. The amount of gold excreted in the stools in a three-day period was 0·66 mg.; in two other cases in which the fæcal excretion was measured it ranged from 0·22 to 0·65 mg. per day. In another case in which 330 mg. of the gold salt had already been given observations were made during a fortnight in which 25 mg. of gold salt were given every seven days. She excreted a total of 4·35 mg. of gold, equal to 17·2 per cent. of the intake; but this proportion does not take note of the 330 mg. previously given.

Excretion was found to persist for long periods after administration had ceased. In the case which received 140 mg. of gold in thirteen days 0·01 mg. was found on the 300th day afterwards.

No excretion in the saliva was discovered in two cases in which this was investigated.

The researches are being continued.

Tarsy (*Journ. Lab. and Clin. Med.*, xxvi., 12, p. 1918), impressed with the value of gold in the treatment of arthritis and at the same time with the frequency of toxic reactions, made a search for some similar or related agent which might incorporate the beneficial therapeutic qualities of gold salts without their serious toxic effects. He and his colleagues found gold sodium thiomalate not quite so reactive as the thiosulphate, and that it could be used in larger doses, although it may be noted that the thiomalate contains 50 per cent. of metallic gold as compared with 37 per cent. in the thiosulphate. In view of the alteration in the activity of colloidal silver as compared with the salts, it was thought that colloidal gold offered definite possibilities, and

in addition colloidal platinum, colloidal bismuth and selenium were at first included in the study, but later abandoned as not giving sufficient promise of usefulness.

Colloidal gold consists of innumerable particles of metallic gold, and indications have been noted in other researches that even in very dilute solutions colloidal gold exerts a definite analgesic action. Colloids when injected into the bloodstream induce a mild shock similar to that which usually follows injection of a non-specific protein.

Thirty-six cases were treated with gold colloid, varying from early mild cases to chronic bedridden patients, and two cases of generalised fibrositis of many years' standing were included. Nineteen, or 52·7 per cent., showed definite improvement, while 9, or 25 per cent., failed to show any amelioration; these figures compared with the statistics of 1,600 cases treated with gold salts with an average marked improvement of about 54 per cent. and total lack of improvement in 13 per cent. The improvement with the colloid was rather slower in developing than with gold salts, but the two cases of fibrositis showed a quick and excellent response.

The technique was three series of injections, each series comprising 1 gm. of metallic gold, an interval of six weeks elapsing between each series. There was an almost complete lack of toxic effects. One case developed enlargement of axillary lymph glands, an effect which has also been noted after the injection of gold salts. There was an improvement in the sedimentation rate parallel with the clinical improvement. There was no evidence of any renal damage. An essential difference was the lack of any bacteriostatic action with colloidal gold contrasted with the very active bacteriostatic effect shown by the sera of patients treated with gold salts.

Study of the reticulo-endothelial system with trypan blue carried out by Kuhns and Weatherford (*Arch. Surg.*, 1936, **33,** 68) indicated that the colloid particles were deposited in the histiocytes of the synovial membrane, the bone marrow, the intermuscular septa and articular fat pads, and it is suggested that the particles of colloidal gold may be similarly deposited.

While no dramatic therapeutic claims are made, it is felt that a case has been made out for further investigation, especially in fibrositis and rheumatoid arthritis of milder types.

"The Effect of Gold Sodium Thiomalate Administration on the Bacteriostatic Properties of the Serum in Patients with Rheumatoid Arthritis" (*Journ. Lab. and Clin. Med.*, xxvi., 8, pp. 1274-84), F. Hartung and Joyce Cotter. These observers studied the bacteriostatic properties of the serum before and after the parenteral administration of gold salts, and also the effect on the agglutinin titres. The patients were cases of rheumatoid arthritis and were treated by weekly injections of 5, 10, 25, and occasionally 50 mg. doses, until a total of 1 gm. had been given. Toxic reactions were frequent—of minor degree in at least a half and of more serious character in 15 per cent.

In the research a strain of beta hæmolytic streptococcus was used; the gold salt was gold sodium thiomalate in aqueous solution administered subcutaneously. In addition, a 1 per cent. metallic gold in colloid suspension was tried, and also 10 per cent. bismuth salicylate in oil. For the technical details the original paper must be consulted, but the essential point is that the serum of patients with rheumatoid arthritis possessed no more bacteriostatic property than did controls before the injection of gold, but even after a small dose it became definitely bacteriostatic, and this property increased with the amount of gold given to a maximum which was reached after 147 to 155 mg. had been given, and did not materially increase even after many times these amounts had been administered. After gold salts had been withheld for from three to six months the bacteriostatic power was found to have been lost. *In vitro*, gold sodium thiomalate was found to be bactericidal in the stronger dilutions and bacteriostatic in the weaker; the addition of whole blood to the extent of 50 per cent. destroyed the bacteriostatic power. Similar results were obtained with several other common laboratory organisms.

No definite effect upon agglutinin titres was detected. Colloidal gold did not produce significant bacteriostasis, and bismuth salicylate was hardly more effective.

"Toxic Reactions with Gold Salts in Treatment of Rheumatoid Arthritis" (*Journ. Lab. and Clin. Med.*, xxvi., 10, p. 1629). R. M. Lintz. In this discussion of the various toxic reactions following the use of gold salts some points are especially worthy of note. The author found in the earlier cases that in almost

every instance the patient experienced a flushing of the face within one or two minutes after receiving the gold compound: the face became fiery red with a sense of heat and often vertigo; but it is worthy of note that this reaction has almost ceased since the method of producing the thiomalate has been changed. With gold sodium thiomalate, though the usual minor toxic reactions and an occasional severe one have occurred, there have been no fatalities; but among a small number who received gold sodium thiosulphate there were two with very severe reactions, one of whom died. The *intravenous* route appeared to be definitely attended with increased risk. In another series in which the maximum single dose of thiosulphate was 0·05 gm., excellent results were obtained with a minimum of toxic reactions, which were of minor character. The number of cases observed was, however, insufficient to justify any definite conclusions.

There are many points of interest and practical importance in these reports. One of the most important appears to be that smaller doses than those which have hitherto been the practice are not only adequate but much less liable to give rise to toxic effects. The possibility that the interval between doses might also be longer is worth exploring. The length of time after completion of a course during which gold continues to be excreted in the urine points to the desirability of a longer interval between the courses. Examination of the urine for gold at the end of three months and at intervals thereafter would seem to be a wise course. It has been the experience of the reviewer that occasionally the first dose of a second course, though small, has given rise to a marked toxic reaction; probably in such cases the rate of excretion has been slow. The further investigation promised by Freyberg and his colleagues as to the possible necessity of a minimal amount of gold in the circulation for a minimal period promises to be of importance.

Another point to be noted is that toxic reactions after a course in which the maximum dose had been not more than 0·25 mg. of metallic gold in the investigations carried out by Freyberg, Block, and Levy were few and slight in character. In Hartung's cases, however, in which a dose of 50 mg. was only occasionally given, toxic reactions appear to have been more frequent; the only difference in method being apparently that in the former the injection was intramuscular and in the latter sub-

cutaneous; the point appears to be worthy of further investigation.

Lintz's observation that certain reactions followed immediately upon injection in his earlier cases (Freyberg observed similar effects in some cases), but ceased to happen when the method of preparation of the injection was altered, appears to indicate that some other factor than metallic gold played a part. It would be interesting to know if this reaction occurred after a first dose or only after later ones; in the latter case an acquired sensitivity to some constituent seems a possible explanation. If this is so, the administration of calcium with the gold which has been advocated by some would seem to be a good practice.

Gold has not hitherto been tried extensively in fibrositis, and the observations of Tarsy would appear to call for a more extensive trial of the colloidal form in suitable cases, preferably those which are apparently due to toxins of bacterial origin rather than to metabolic or traumatic causes. This is important in view of the probability that the diagnosis of fibrositis is made in cases of widely differing nature and ætiology.

While the bacteriostatic action of gold in the plasma must be regarded as of great importance, the fact that colloidal gold was found by Tarsy to be effective in a good proportion of cases, while no bacteriostatic effect could be detected in the serum, seems to indicate the importance of some other mode of action in addition.

The fact that some of the researches which have been discussed are still being carried on justifies the hope that the value of chrysotherapy will be clearly demonstrated apart from clinical experience, and that sound principles for its use will be established.

C. W. Buckley.

Effect of Influenza Virus on the Hæmolytic Streptococcus.

There would appear to be abundant evidence that streptococcal infection of the upper respiratory tract, especially of the tonsils, may be closely associated with the genesis or recrudescence of rheumatism. Factors influencing the pathogenicity of this streptococcus, therefore, are of special interest because of their possible importance for arriving at a correct interpretation of the present evidence concerning the ætiology of rheumatism.

In a recent contribution to the *British Journal of Experimental Pathology* (1941, **22**, 91-107) C. H. Andrewes and R. E. Glover describe the result of an experimental study of the conditions under which influenza produced in the ferret by human virus A is transmitted through the air. When material containing the influenza virus is instilled into the nares of the ferret, that animal after an incubation period duly develops the disease, proof of which is afforded by the temperature response, symptoms, and if need be by an immunity test. Careful experiments indicated that in still air, such as obtains in cubicles when windows and doors are closed, influenza virus could spread through the air from the respiratory tract of one ferret to that of another for a distance of 5 feet on the level, and even for 3 feet above the cage in which the "donor" ferret reposed. Screening and dilution of the air by opening the window appeared to reduce the risk of infection; but further observations on this are needed.

In the pandemic of influenza of 1918-19 that spread over the world and is estimated to have killed twenty million people, an increase in the severity of the disease in man was frequently observed when the hæmolytic streptococcus became involved in the infection. It is of particular interest, therefore, that in course of the transmission of influenza virus A through the nasal passages of a series of ferrets Andrewes and Glover encountered a similar increase in the severity of the disease when a hæmolytic streptococcus was found to be co-operating with the virus. The opportunity was taken by Glover to study the part played by this streptococcus in the combined infection, and also the extent to which it was sprayed out into the surrounding air by an affected ferret. The streptococcus belonged to Lancefields Group C, and in Glover's view it was probably present in the respiratory tract of one of the ferrets in the transmission series, being stirred into activity by the influenza virus and carried on by the subsequent passage.

By instilling cultures of this hæmolytic streptococcus into the nares of ferrets and then sampling their nasal secretion, Glover found that by itself this streptococcus was incapable of infecting the nasal mucosa. On the other hand, when influenza virus was also present, the streptococcus established itself on the nasal mucosa with ease and flourished there. Similarly, when normal ferrets were placed in close contact with doubly infected ferrets the streptococcus invariably established itself

in their noses, and when the animals were separated by an air barrier of 4 feet the streptococcus failed to infect normal ferrets, but did infect the nasal passages of those suffering from influenza A. A further point of interest was that when the presence of the virus enabled the streptococcus to become established, the streptococcus could be recovered from the nasal mucosa, the turbinates, and also from the tonsils in which it appeared to persist longest.

A previous experimental study of the effect of a virus on the pathogenicity of the hæmolytic streptococcus was reported in a preceding number of the ANNALS (1939, vol. i, No. 1). The animal used was the rabbit, the route of injection the vein, and the lesion produced arthritis. The virus employed was the M4 strain of vaccinia of Tulloch with its pathogenicity brought to the maximum by recent passage and repeated dose. Foci of periarticular fibrositis were produced in the rabbit in which lymphocytes predominated and the virus was present in large numbers. In course of these observations definite evidence was found that the virus increased the pathogenicity of the streptococcus, and *vice versa*. In the tissues infected by a mixture of the two the virus appeared to be the stronger, the streptococcus disappearing. The suggestion was made that something similar might be taking place in acute rheumatism. The present observations of Andrewes and Glover, however, are of far more interest because there the normal nasal mucosa was the testing ground, and the other conditions were a closer approximation to those obtaining in man at the onset of rheumatism.

M. H. G.

EMPIRE RHEUMATISM COUNCIL

FIFTH ANNUAL REPORT

NOVEMBER, 1940, TO NOVEMBER, 1941.

My Lords, Ladies and Gentlemen,

This is the third year in succession that I shall not have the pleasure of meeting you for discussion of the Annual Report. I regret the long lapse, for there is nothing more valuable to an organisation such as ours than personal contact and free debate among members. But it was considered inadvisable under war conditions to make demands on your time and on transport services by calling members of the Council to London. I submit to you the Annual Report to November, 1941.

Our President, H.R.H. the Duke of Gloucester, acknowledging the Report for 1940, expressed his pleasure that "the War on Rheumatism is being bravely and vigorously carried on" and added: "Please accept for yourself and convey to your colleagues and fellow-workers my congratulations on the good work of the past year, and my confident hopes of full success in the future."

The completion of the fifth year of our campaign suggests a brief retrospect. At our first Annual Meeting I outlined two programmes to be followed concurrently; with the hope that one, as regards treatment, would be for a short term; with the warning that the other, as regards research, would be for a longer term. At that date one could not foresee the destructive war which the fermenting of a morbid mind, finding a favourable medium in a morbid people, was about to inflict on mankind. That war has affected every humane activity. Ours was not excepted. The effect, however, has been to delay, but not to thwart, our plans. Viewed in the light of the vast events which have shaken the world, the large measure of attention we have won for a long-neglected problem of public health, and in particular the good progress of last year, is reason for reassurance.

To note the development of our two programmes:

Treatment

Publication, early this year, of *Rheumatism—A Plan for National Action*, in the preparation of which I had the valuable

collaboration of members of our Council, brought a notable awakening of public interest to the serious lack of facilities for effective treatment of Rheumatic Disease. The practical and reasonably economical scheme for remedying this which was outlined has stood the test of close examination by the medical and lay Press. There was no adverse criticism, but a general recognition that the damage to human well-being caused by Rheumatic Disease could, and should, be checked.

It may be stated, I think, that our Council has now fulfilled in large measure one important part of its duty—viz., to survey the position in regard to Rheumatism Treatment in the present state of medical knowledge and to show how action, on a scale comparable with that taken against other social plagues, could effect a prompt and great reduction in the number of lives now wrecked by its ravages.

The task still faces us of persuading the community, working through its appropriate authorities, to take action. They at any rate now know the nature of the task, and can see that it is not an impossible one. If the sight of means to do good deeds will make good deeds done, national and local administrators will see that the time to plan against Rheumatic Disease is *now*, even if some of the necessary measures must be postponed until peace conditions return.

There are several favourable facts to record in regard to the provision of effective means of treatment.

In March, Mr. James Currie Macbeth, Chairman of the Carnegie Dunfermline Trust, wrote to me with reference to the publication mentioned, " For many years I have considered that some national effort should be made with a view to minimising the loss in this country through rheumatic disease." He indicated that the Trust would be willing to consider helping such an effort. Sir Frank Fox visited Dunfermline and met Mr. Macbeth, some of his co-trustees, and Dr. Emslie Smith, Medical Officer of the existing Children's Clinic of the Trust. In negotiations which followed, Mr. Macbeth showed a cordial desire that the Trust should take action in the Burgh of Dunfermline against Rheumatic Disease commensurate with the excellent standard of its other work there for social welfare. The " cordial approval " of this by the Carnegie Dunfermline Trust was notified in August. Professor Stanley Davidson and Sir Frank Fox have been entrusted by the War Emergency Com-

mittee with the formulation of a detailed plan for discussion with the Trustees.

In May we learned that the late Miss Margaret Ann Cran, of Aberdeen, by her will, made a bequest of £1,000 and the residue of her estate (this residue estimated to yield about £9,000) for the purposes of a hospital or clinic for the treatment of rheumatism in Aberdeen, "preferably on the lines indicated by Professor Stanley Davidson," but subject to the approval of the Executory, to be established within five years after her death.

Professor Davidson and Sir Frank Fox (who have been entrusted with the negotiations) have seen Mr. Alexander Clark, advocate, acting for the Executory, and there is no doubt that our Council will be able to submit to the Executory a plan for an Aberdeen treatment centre, fulfilling the intention of the testatrix.

The Red Cross Rheumatism Clinic, the St. John Clinic, the West London Hospital Rheumatism Clinic, and other clinics in London, the Spa hospitals, and the few other treatment centres in the kingdom, continue their work, and the extent of the demand on their services shows how much it is valued.

So much is favourable, but it would be idle to pretend that this represents more than a gleam of promise on an otherwise dark picture. The position continues to be that only a small proportion of sufferers can obtain in the early stages of Rheumatic Disease the right diagnosis and the right treatment, which would save a very great proportion from becoming disabled. We have a constant stream of letters from sufferers asking where they can get advice and effective treatment in their neighbourhood; the answer must be generally disappointing. We hear of the absurdity that members of an Approved Society giving rheumatism treatment benefit are deprived of that benefit because of the impossibility of incurring travelling expenses and loss of time to reach a distant treatment centre.

We must press for national action based on recognition of the facts that Rheumatic Disease is the greatest single enemy of social well-being and economic efficiency in our land; that, in the present state of medical knowledge, it can be very largely diminished; and that the cost of the necessary measures by national and municipal authorities and by industrial organisations would be so moderate as to make them well worth while as a matter of economy, apart from considerations of humanity.

Research

To come now to our longer-term programme, research into causative factors. This, as reported to you last year, has had serious checks: the closing of one laboratory; the destruction of another laboratory by enemy action. But, nevertheless, much valuable work has been carried out, mainly in the search for the cause of acute rheumatism and for a definite test, serological or biochemical, of the rheumatic condition. Discovery in the first field would probably throw light upon other morbid conditions now classified in the rheumatic group of diseases. Discovery in the second field would clear away existing difficulties of accurate diagnosis.

The work of the Naval Research Foundation (Dr. C. A. Green, Director) makes excellent progress. The engagements of Dr. Green and of Professor Ernst Freund (Director of the section at the West London Hospital) have been extended for one year.

Dr. Green has submitted a comprehensive report on his investigations. The subject-matter of this report was submitted by him to Edinburgh University as his thesis for the M.D. degree. That degree was awarded him, also the degree of Ph.D. and a gold medal.

The Sir Halley Stewart Trust have renewed for a further year its financial grant to this Foundation. I take this opportunity to record again our cordial thanks to them, and to Mr. Frederick A. Pearson, for generous help; and our appreciation of the cordial co-operation of the Admiralty Medical Services and of the group of scientists who are giving distinguished assistance—chiefly Dr. Mervyn Gordon, Professor G. Hadfield, Professor J. T. Mackie, Professor J. W. McNee and Lt.-Colonel W. S. C. Copeman.

Dr. C. B. Dyson, Research Fellow at our Sir Alexander Maclean laboratory, Hospital of St. John and St. Elizabeth, accepted a post in the north as a general practitioner. Enthusiasm for research led him to offer to continue there, as far as practicable, his task. This offer was gladly accepted, and the equipment of the laboratory temporarily transferred to him. His work, which is honorary (our Council meeting the expenses incurred), is assisted by Dr. Margaret Green.

Dr. Cecilia Lutwak Mann has continued her work at the University of Cambridge School of Biochemistry, and this year published a paper on " Enzymic Decomposition of Amino-Sugars."

In the field of clinical research, good work has been done: testing techniques for local injection in the treatment of fibrositic forms of rheumatism; investigation of the results of treatment of rheumatism by gold salts, etc. Clinical research work is, however, seriously hampered by the lack of treatment centres which can undertake investigations under the necessary control conditions of (*a*) careful preliminary diagnosis, following an agreed standard classification of the forms of Rheumatic Disease, and (*b*) clear record of clinical results, following again a standard form. The Council is hopeful, as new treatment centres are established, of greater progress in clinical research.

Official Journal

Our official journal, *Annals of the Rheumatic Diseases*, has maintained its high standard, publishing important papers by British and American authors. During the year Dr. Loring T. Swaim, M.D., President of the American Rheumatism Association, accepted an invitation to join the Editorial Committee as American Editor. This is another instance of the growth of cordial co-operation between American and British scientists in the war on rheumatism. The Editorial Committee now consists of C. W. Buckley, M.D., F.R.C.P., W. S. C. Copeman, M.D., F.R.C.P., A. G. Timbrell Fisher, M.C., F.R.C.S., Mervyn Gordon, C.M.G., F.R.S., and Loring T. Swaim, M.D.

Education

The year has seen notable progress in our educational work. Despite preoccupation of public interest in that other war, our war on rheumatism won more Press attention than at any period since 1937. The total number of articles and reports in important British and American papers during the year numbered some 200, most of them lengthy. Since practically all British publications have been reduced to half their normal size by war conditions, this is a gratifying record. Sincere thanks are due to the "Fourth Estate of the Realm" for recognition on its part of the humanitarian and economic importance of our work.

From the United States of America there has come cordial appreciation of the last Annual Report by leading rheumatologists and medical journals. One of the latter, in a leading article, expressed the hope that the British effort " should stir

our country to do likewise." To be credited with setting an example to the great Republic is high praise.

I was happy to accept an invitation to sponsor, on behalf of our Council, a movement to establish in Massachusetts a Rheumatism Treatment Centre on the lines we advocate.

Work for the Armed Services

I have little to add to my report last year on this matter. We continue to do all that is in our power to help Navy, Army and Air Force with their problems arising from Rheumatic Disease, and gratefully recognise an increasing degree of willingness to accept our co-operation.

Administration

The death of Sir William Willcox in July last was a grievous loss to our Council. I know that all members will join with me in recording grateful appreciation of his services and sympathy with his family. In the course of a long and distinguished career as a physician there was perhaps no service for the public good which more closely engaged his sympathy than the work of the Empire Rheumatism Council. From its foundation he acted as a Trustee, as Chairman of the Executive Committee and as Chairman of the Research Advisory Committee. In all these offices his knowledge, his tact and his human sympathy were of the highest value.

Mr. A. G. Timbrell Fisher was left by this loss as the sole surviving Trustee. The War Emergency Committee considered it advisable to increase the number of Trustees to four. Col. the Rt. Hon. John Gretton, M.P., Sir Walter Kinnear and Lt.-Col. W. S. C. Copeman agreed to act and have been duly appointed. I have myself undertaken the chairmanship of the War Emergency Committee. Since the Research Advisory Committee is not meeting during the War Emergency, it is proposed to postpone the appointment of a new Chairman until peace conditions return.

In May it was decided to remove our headquarters from the Temple to a temporary office at 326, Finchley Road, London, N.W.3. The decision was not lightly taken. Attacks by the New Barbarism on the Temple were frequent, and the effects of explosive and incendiary bombs in January, March and May had left our office still standing in a scorched remnant of its

building, but a move was considered advisable. All our records and property were undamaged and there was no interruption of work.

The Council will wish to place on record again its appreciation of devoted zeal in your work during the year by members of the War Emergency Committee—viz., Dr. C. W. Buckley, Lt.-Col. W. S. C. Copeman, A. G. Timbrell Fisher, Dr. Mervyn H. Gordon, Col. the Rt. Hon. John Gretton, Col. F. D. Howitt, Sir Walter S. Kinnear, T. W. Robinson, H. Gordon Thompson. The Committee has met as often as necessary. Good staff organisation—obtaining decisions in certain matters by postal vote and in other matters seeking consultations with individual members of the Committee—has kept down the number of meetings. There is in our work, as you will know, a great amount of negotiation and correspondence—great in bulk and intrinsic importance—and many possible pitfalls. I have reason for confidence that the work is carried out with care and discretion by our wise and energetic organising Secretary, for whom no praise is too high.

I leave to the Finance Members of the War Emergency Committee to report on our financial position, noting only that this year we have done considerably better than in the two previous years. Our cordial thanks are due to those who have steadily continued their support and to others who have joined the ranks of our good providers. The Prudential Assurance Company, with its Approved Society, by the extent of its wise and public-spirited aid to the War on Rheumatism—coming second only to that of our first large benefactor, Sir Alexander Maclean—has given a splendid example to other great national organisations in supplying the munitions for that war.

Munitions are essential. You cannot wage war without them. But I know you will agree with me in withstanding any tendency to give undue importance to money-collecting. What we ask is the investment by the community of a sum, really insignificant in view of the benefit to be reaped, for bringing Rheumatic Disease under control. It is not material what portion of that sum passes directly through our books; the important thing is that it should be spent wisely.

The Future

At our first Annual Meeting, in acknowledging a vote of thanks, I ventured the apophthegm "That the Empire Rheumatism Council

would best justify its existence by bringing that existence to an end as soon as possible." My intention was to impress that our task was one of urgency and also one of distinct hopefulness. The date for the end of our existence can be defined as the date on which Rheumatic Disease is brought under control; effective treatment available for all; research, if not yet successful in all its quests, sufficiently endowed for any tasks remaining to be done. I believe that we are on the threshold of the first objective. The second objective will engage us for a longer term. But there are promising indications that it will be a reasonable term. Certainly I do not envisage such a period as elapsed between the time when Herodotus acutely observed that the fishermen of the Nile delta suffered relatively less than others from the prevalent malaria, and guessed that it was because the nets they hung to dry over their huts "kept out the malarial air." It took many centuries to discover that, by the change of one word, "mosquito" for "air," there was the key to the control of the greatest of the tropical scourges. We may confidently expect that discovery of the key to the causation of Rheumatic Disease will be a matter of years, not of centuries.

(*Signed*) HORDER.

FINANCE REPORT

Last year the hope was ventured that new subscriptions during 1941 would be greater than in the previous year (when we refrained from any general appeal to leave the field clear for the urgent claims of war charities). The hope was realised. New subscriptions totalled £3,946 in cash or covenants. In addition we may rely in the near future upon a sum of over £10,000 from an Aberdeen bequest, and a sum, which cannot yet be estimated, from the Dunfermline Carnegie Trust. These results are encouraging for the future, but much larger resources should be available for the post-war period if we are to continue our research work and take our rightful part in securing a national plan of treatment.

Financial administration during the past year has had to meet special difficulties as the result (1) of various changes in financial legislation and (2) of enemy action. We acknowledge again with thanks the helpful attitude of the Charity Claims Department of the Inland Revenue. The special provision in the Finance Act, 1941, regarding Seven Years Bonds will not

prejudicially affect our interests; this because from the outset we adopted a form of covenant departing from the more usual form but designed to meet the possible contingency of changes in the rate of Income Tax.

Careful economy has been observed, but we thought it desirable to modify somewhat the sacrifices volunteered by the staff on the outbreak of the war. Our small Reserve Fund has been increased by £2,125. It is invested at from 2½ to 3 per cent. in Government securities which cannot depreciate in capital value and are fully liquid.

This year closes the first quinquennium of the Council's work. A brief survey of the whole financial position may be useful. At the outset we planned for a revenue of £150,000 within seven years. The first year, when subscriptions totalled just on £25,000, was encouraging. Then (1938) came war forebodings. In that year the value of the 365 " key securities " on the London Stock Exchange fell by £270,000,000, the lowest since 1933. The effect of this (and later of the outbreak of war) on charity subscriptions was great. Up to November, 1940, our total subscriptions had reached only £48,822. The 1941 results showed a recovery, as noted. It is, perhaps, not too much to hope for that our preliminary budget of £150,000 may be realised within a ten, instead of a seven, years' period and that within that term the purpose of the Council will be to a large extent achieved.

(*Signed*) T. W. Robinson,
W. S. Kinnear.
(*Finance Members of the War Emergency Committee*).

AWARDS FOR PHYSICAL THERAPY

The Empire Rheumatism Council have been informed by the American Congress of Physical Therapy for 1941:

" In recognition of distinguished contributions to the medical science of physical therapy, Gold Key awards were made to four world-renowned individuals by the American Congress of Physical Therapy. First of the four men was President Franklin D. Roosevelt, to whom a key was presented in appreciation and recognition of his long interest and support of the medical fight against infantile paralysis. The other three men singled out

for their distinguished service to physical therapy were Dr. William Bierman, New York specialist, faculty member of New York University and attending physical therapist at Mount Sinai Hospital in New York; Lt.-Col. W. S. C. Copeman, eminent scientist of London, England, and honorary secretary of the British Rheumatism Council; and Bernard M. Baruch, noted industrialist and financier. . . .

"Lt.-Col. W. S. C. Copeman, of London, England, author, executive, scientist, and physical therapist, was honoured for his recent contribution to the advancement of physical therapy in developing a remarkable military physical therapy organisation in the field under the most unfavourable conditions. Lt.-Col. W. S. C. Copeman's description of his improvisation of physical therapeutic equipment during actual warfare has so greatly impressed the American Congress of Physical Therapy that special recognition was given by the American organisation to this English associate."

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Supplies:

Ampoules of 0.01 Gm. at 1s. 9d.
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In aqueous solution or oil suspension.
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Injections of 0.01, 0.02 and 0.05 gramme are given, and if there is no sign of intolerance, the treatment is continued with 0.10 gramme weekly until approximately 1 gramme has been administered in 10-12 weekly injections. Whatever degree of improvement results, relapse will occur unless further treatment is given, but 12 weeks' rest period must be allowed between courses.

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'ANADIN' TABLETS produce their effect by a judicious combination, in small but adequate quantities, of four proven anodyne and analgesic drugs, acetphenetidin, acetylsalicylic acid, caffeine alkaloid and quinine sulphate.

There is in this way no risk attached to repeated administration. The quinine and caffeine maintain cardiac tone and diuresis, in addition to contributing an antipyretic factor.

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